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# CULTURALLY INFORMED HEALTHCARE SYSTEMS AND FUNCTIONAL THERAPEUTIC DEVELOPMENT

EDITOR

Dr. Alejandro Mustieles Ocaña

# CULTURALLY INFORMED HEALTHCARE SYSTEMS AND FUNCTIONAL THERAPEUTIC DEVELOPMENT- 2026

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# CULTURALLY INFORMED HEALTHCARE SYSTEMS AND FUNCTIONAL THERAPEUTIC DEVELOPMENT

**EDITOR**
Dr. Alejandro Mustieles Ocaña

**AUTHORS**
Aisyah Dini RAHMAWATI
Meerab WASEEM
Wafa MAJEED
Kashif JILANI
Ayesha
Khadija ALMAS
Arie Febrianto MULYADI

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## PREFACE

This volume brings together a collection of scholarly contributions that explore the evolving landscape of healthcare systems, clinical practice, and therapeutic innovation. In an era where health services are shaped by cultural, technological, and scientific developments, integrative approaches have become increasingly important for addressing complex health challenges.

The chapters in this book address key themes across health policy, clinical medicine, and pharmaceutical development. The examination of halal medical service policies highlights the role of ethical, cultural, and economic considerations in shaping contemporary healthcare systems. The discussion on musculoskeletal pain provides valuable insights into the pathophysiological mechanisms underlying acute and chronic conditions, contributing to improved clinical understanding and patient care. In addition, the development of plant-based functional supplements reflects the growing importance of natural products and innovative formulation strategies in modern therapeutics.

By adopting an interdisciplinary perspective, this volume integrates insights from health policy, clinical sciences, and pharmaceutical research. It contributes to academic discourse while also offering practical implications for healthcare professionals, researchers, and policymakers working to develop inclusive, effective, and innovative healthcare solutions.

It is hoped that this book will serve as a valuable resource for scholars and practitioners interested in healthcare systems and therapeutic innovation, while encouraging further research at the intersection of policy, science, and integrative medicine.

**Editorial Team**
**May, 2026**
**Türkiye**

# CHAPTER 1
# ECONOMIC TRANSFORMATION OF ISLAMIC DEVELOPMENT IN THE HEALTH SECTOR: A QUALITATIVE ANALYSIS OF HALAL MEDICAL SERVICES POLICY IN INDONESIA

[1]Aisyah Dini RAHMAWATI

[1]Universitas Islam Negeri K.H. Abdurrahman Wahid Pekalongan, Indonesia, aisyah.dini.rahmawati@mhs.uingusdur.ac.id, ORCID ID: 0009-0008-6689-8120

## INTRODUCTION

The development of Islamic economics in recent decades shows a transformation that is not only quantitative but also qualitative. In the early stages of its development, Islamic economics was more focused on the formation of a financial system that was free from the practices of riba, gharar, and maysir in response to the dominance of the conventional financial system, which was considered not in line with sharia principles. These efforts have given birth to various Islamic financial institutions such as Islamic banks, Islamic insurance, and Islamic capital markets, which are currently growing rapidly in various countries, including Indonesia. However, these developments do not stop at the financial sector alone, but have experienced significant expansion into the real sector.

This transformation reflects a paradigm shift in understanding Islamic economics. Islamic economics is no longer seen only as an alternative to the financial system, but as a comprehensive economic system that covers all aspects of human life. This is in line with the basic principles of Islam, which are universal and cover all dimensions of life, including economic, social, and cultural activities. In this context, the application of sharia values not only aims to achieve economic efficiency but also to realize social justice and sustainable welfare.

Along with the increasing awareness of Muslims on the importance of applying Sharia values in daily life, there has been a shift in people's consumption preferences. The public no longer only considers quality and price aspects in choosing a product or service, but also pays attention to the halal aspect and its conformity with Sharia principles. This phenomenon has driven the emergence of various innovations in the halal industry, which not only includes food and beverages but also extends to the cosmetics, fashion, tourism, and health sectors. Thus, the halal industry is developing into one of the strategic sectors in the global economy.

In this context, the health sector is one of the fields that is starting to receive attention in the development of the Islamic economy. This is inseparable from the awareness that health is a basic human need that has a close relationship with quality of life and economic productivity.

Individuals who are physically and mentally healthy have a better ability to contribute to economic activities, so health is one of the important factors in the economic development of a country. Therefore, the development of quality health services is a priority in an effort to improve people's welfare.

Nevertheless, in an Islamic perspective, health is not only understood as a condition free from disease, but also includes a balance between physical, mental, and spiritual aspects. This concept emphasizes the importance of a holistic approach in health care, which focuses not only on curing diseases but also on prevention efforts and improving the overall quality of life. In this case, ethical and spiritual values are an integral part of the healthcare system.

In line with this, health services are no longer seen solely as a technical medical activity, but as part of a life system that must be in harmony with moral and ethical values. The interaction between medical personnel and patients is not only based on professional relationships but must also reflect the values of humanity and justice. In this context, the concepts of halal and thayyib become relevant as a foundation in the development of health services that are not only medically safe, but also in accordance with sharia principles.

Indonesia, as a country with the largest Muslim population in the world, has a very strategic position in the development of the sharia-based health sector. Based on demographic data, the majority of Indonesia's population is Muslim, which directly creates a large domestic market for halal products and services. In addition, increasing public literacy regarding the importance of halal products also contributes to the growth of demand for health services in accordance with Sharia principles.

This phenomenon can be seen from the increasing public attention to the halalness of pharmaceutical products, such as medicines and vaccines, as well as the medical services used. The public is increasingly critical in questioning the origins of the ingredients used in health products, including their production and distribution processes. This shows that the concept of halal is no longer understood narrowly, but has evolved into a part of the halal lifestyle that encompasses various aspects of modern life. The emergence of the concept of halal medical services is a response to this dynamic.

Halal medical services can be understood as a health service system that integrates sharia principles into all aspects of services, from the use of medical materials and products, service procedures, to the governance of health institutions. This concept not only emphasizes the normative aspect of halal but also includes the dimensions of ethics, professionalism, and social responsibility.

In practice, halal medical services include various interrelated elements. One of the main elements is the use of halal pharmaceutical products, which are free from prohibited ingredients and produced through a process in accordance with sharia standards. (Hussaana et al., 2023) In addition, medical procedures must also consider Sharia aspects, especially in certain cases that have implications for Islamic law. On the other hand, hospital governance must also reflect Islamic values, such as transparency, justice, and benefit-oriented services.

Although this concept offers a comprehensive approach, its implementation in Indonesia still faces various challenges. One of the main challenges is the lack of regulations that specifically regulate halal standards in health services. Although the government has issued Law Number 33 of 2014 concerning Halal Product Assurance, its implementation is more focused on the food and beverage sector, while the health sector has not received adequate attention.

In addition, the complexity of the health sector is a factor that complicates the implementation of halal medical services. Health services involve various parties with different interests, ranging from the pharmaceutical industry, medical personnel, hospitals, and supervisory institutions. Coordination between parties is a challenge in an effort to create an integrated system. On the other hand, halal standards in health services have also not been fully accommodated in the national accreditation system, so their implementation is still partial and non-uniform.

Another challenge is the limited number of human resources who have the competence to integrate Sharia principles into medical practice. Medical personnel in general focus more on the clinical aspect, so their understanding of Sharia principles is still limited.

This shows the need to develop an education and training curriculum that is able to bridge the gap between medical science and Sharia values.

On the other hand, the limitation of supporting infrastructure is also an obstacle to the development of halal medical services. For example, the availability of halal pharmaceutical products is still limited, both in terms of quantity and variety. This is due to the complexity of the production process and the limitation of raw materials that meet halal standards. In addition, the halal certification system for health products is also still in the development stage, so it has not been able to accommodate all industrial needs.

However, in the midst of these challenges, the opportunity for the development of halal medical services in Indonesia is huge. This is driven by increasing public awareness of the importance of health services in accordance with Sharia principles, as well as government support in the development of the halal industry in general. In addition, technological developments also open up opportunities to improve the efficiency and quality of halal-based health services.

At the global level, the halal industry shows a very rapid growth trend, including in the health sector. Countries such as Malaysia have first developed the concept of sharia hospitals and halal medical tourism as part of the national economic strategy. Malaysia's success in developing this sector shows that halal medical services have not only religious value, but also significant economic value. This is a challenge as well as an opportunity for Indonesia to strengthen its position in the global halal industry.

From an economic perspective of Islamic development, the development of halal medical services has a very strong relevance. Health services are part of the effort to protect the human soul (hifz al-nafs), which is one of the main goals in maqashid al-shariah. Therefore, the development of this sector not only aims to increase economic growth but also to realize the welfare of the community holistically.

Furthermore, halal medical services also have the potential to be a catalyst in the development of the overall halal industry ecosystem. This sector has linkages with various other industries, such as pharmaceuticals, food and beverages, and medical tourism. Thus, the development of a halal-based health sector can have a significant multiplier effect on the national economy.

However, it is important to note that the development of halal medical services should not be only symbolic or simply labeled. There is a risk that this concept is only used as a marketing tool without being followed by substantive implementation. Therefore, strict supervision and commitment from all stakeholders are needed to ensure that sharia principles are truly implemented in practice.

Based on this background, this chapter aims to analyze in depth the halal medical services policy in Indonesia and its implications for the economic transformation of Islamic development. This chapter uses a qualitative approach with a literature study method to examine various regulations, research results, and relevant industry reports. Through this analysis, it is hoped that a comprehensive understanding of the actual conditions, challenges, and opportunities in the development of halal medical services in Indonesia can be obtained.

In addition, this chapter also aims to contribute to the development of Islamic economic studies, especially in the health sector, which is still relatively under-attention. With a more in-depth study, it is hoped that more effective policy recommendations can be produced in supporting the development of halal medical services as part of the Islamic economic development strategy in Indonesia.

Ultimately, the development of halal medical services is not only a market need, but also part of efforts to realize a more equitable, sustainable, and well-being-oriented economic system as a whole. Therefore, synergy is needed between the government, industry, academia, and society in developing this sector in an integrated and sustainable manner.

## 1. DISCUSSION

The concept of halal medical services is a form of innovation in the development of the Islamic economy that shows a paradigm shift from the financial sector to the real sector, which is more complex and multidimensional. In this context, the integration between sharia principles and modern health services is not only a normative need for Muslim society, but also an economic strategy that has great potential in encouraging the growth of the halal sector as a whole.

Halal medical services not only provide health services that are free from haram elements, but also seek to build a health service system based on comprehensive Islamic ethical values.

From the perspective of Islamic economics, every economic activity must be oriented towards the achievement of benefits (maslahah), which includes worldly and ukhrawi dimensions. The principles of justice (adl), transparency (amanah), and balance (tawazun) are the main foundations in carrying out economic activities, including in the health sector. Therefore, health services are not only seen as technical activities that aim to cure diseases, but also as part of worship that must be carried out in accordance with Sharia principles. This requires a paradigm shift in looking at the health sector, from profit-oriented to value-oriented, that prioritizes humanitarian and spiritual aspects.

Halal medical services include various integrated dimensions, each of which has its own complexity. One of the most fundamental aspects is the use of halal pharmaceutical products. In practice, the global pharmaceutical industry still faces various obstacles in ensuring the halalness of products, especially due to the use of raw materials derived from certain animals or chemical substances whose halal status is still debated. In addition, the drug production process involves various stages, from research and development to distribution, which adds complexity in ensuring that the entire supply chain meets halal standards.

The limitation of halal raw materials is one of the main obstacles in the development of halal pharmaceuticals. Many of the active ingredients in medicine come from sources whose halalness cannot be guaranteed, such as gelatin taken from non-halal animals. On the other hand, the substitution of such materials often requires high research costs and a short time. This causes the price of halal pharmaceutical products to tend to be more expensive than conventional products, which can affect people's access to halal-based health services.

In addition to the material aspect, the halal certification system is also a crucial issue in the development of halal medical services. Halal certification not only serves as a guarantee for consumers but also as a regulatory instrument that can encourage quality standards in the health industry.

However, the complex and cost-effective certification process is often an obstacle for industry players, especially for small and medium-sized companies. Therefore, a policy is needed that can simplify the certification process without compromising its quality and credibility.(Hakim & Anggraeni, 2023)

In addition to pharmaceutical products, the aspect of medical procedures is also an important component of halal medical services. In modern medical practice, there are various actions that require ethical and legal considerations from an Islamic perspective. For example, organ transplantation, the use of assisted reproductive technology, and medical procedures involving certain biological materials. In this case, fatwas from religious institutions are the main reference in determining the ability of a medical action.

However, the implementation of fatwas in medical practice does not always go smoothly. One of the main challenges is the difference in interpretation of the fatwa, both among scholars and medical personnel. In addition, the rapid development of medical technology often exceeds the ability of regulations and fatwas to keep up. As a result, there is a gap between the development of science and the existing legal framework, which can create uncertainty in medical practice.

Hospital governance is also an equally important element in the concept of halal medical services. Sharia hospitals are not only required to meet high medical standards, but must also be able to integrate Islamic values in all aspects of their operations. This includes sharia-based financial management, patient satisfaction-oriented services, and a work culture that reflects Islamic values.

In practice, the implementation of sharia-based governance requires fundamental changes in organizational structure and management systems. For example, in the financial aspect, Islamic hospitals must avoid the practice of usury and apply the principle of profit sharing in fund management. In the service aspect, medical personnel are required to not only provide professional service but also show a high attitude of empathy and concern for patients. The transformation of conventional hospitals into sharia hospitals is a complex process and requires a strong commitment from all stakeholders.

This process involves not only changes to operational standards, but also changes in organizational culture. One of the main challenges in this process is resistance to change, especially from medical personnel who have become accustomed to conventional systems. Therefore, an effective change management strategy is needed to ensure the success of such transformations.

In terms of policy, the Indonesian government has shown its commitment to developing the halal industry through various regulations that have been issued. However, existing policies still tend to be partial and have not been fully integrated. This can be seen from the lack of a national standard that specifically regulates halal medical services. As a result, implementation in the field is still highly dependent on the initiatives of each institution, resulting in variations in service quality.

Limited human resources are one of the biggest challenges in the development of halal medical services. Medical personnel who have an understanding of Sharia principles are still very limited, so the integration between medical science and Islamic values has not run optimally. In addition, the medical education curriculum in Indonesia still does not accommodate many Sharia aspects, so reforms are needed in the education system to produce competent medical personnel in this field.

The lack of research and development in the field of halal pharmaceuticals is also an obstacle to the development of this sector. Until now, the number of research studies focused on the development of halal drugs is still very limited, both in terms of quantity and quality. This shows that this sector is still not a priority in the national research agenda, even though it has huge potential to be developed.

On the other hand, the opportunity for the development of halal medical services is huge, especially in the context of the global economy. With increasing public awareness of the importance of halal products, the demand for sharia-based health services is expected to continue to increase. This opens up opportunities for Indonesia to become a major player in the world's halal industry, especially if it is able to develop an integrated halal ecosystem. From an economic perspective of Islamic development, halal medical services have a strategic role in improving people's welfare.

Quality health services in accordance with Sharia principles can improve the quality of life of the community, which will ultimately have an impact on economic productivity. In addition, this sector can also create jobs and encourage the growth of related industries, such as pharmaceuticals, halal cosmetics, and medical tourism.

The development of halal medical services also has significant social implications. Sharia-based health services can increase public trust in the health system, especially for community groups that have high sensitivity to halal issues. This can encourage increased access to health services, which will ultimately have an impact on improving the overall health of the community.

The concept of maqashid al-shariah provides a very relevant framework in the development of halal medical services. One of the main goals of sharia is to preserve the soul (hifz al-nafs), which is in line with the main purpose of health services. In addition, the aspects of maintaining reason (hifz al-aql) and maintaining offspring (hifz al-nasl) also have relevance in the context of health. Thus, the development of halal medical services not only has economic value, but also has very high moral and spiritual value.

However, the development of halal medical services should not stop at the symbolic aspect. There is a risk that this concept will only be used as a marketing tool without substantive implementation. This phenomenon is often referred to as "halal washing", where halal labels are used to attract consumers without any real commitment to sharia principles. If this is not controlled, it can damage the credibility of the halal industry as a whole.

Therefore, a strict supervisory system and an ongoing evaluation mechanism are needed to ensure that the implementation of halal medical services is truly in accordance with Sharia principles. The role of halal certification bodies is very important in this regard, not only as a certifier, but also as a supervisor who ensures compliance with the standards that have been set. Strategically, the development of halal medical services requires an integrated and comprehensive approach. The government needs to play an active role in formulating policies that support the development of this sector, including in terms of regulations, incentives, and human resource development. On the other hand, industry players must also have a strong commitment to consistently apply Sharia principles in their operations.

If analyzed more deeply, the biggest challenge in the development of halal medical services actually lies not only in the technical aspect, but also in the mindset aspect. As long as halal is still seen as an add-on and not as an integrated value system, the development of this sector will run slowly and not optimally. Therefore, a fundamental paradigm shift is needed in seeing the concept of halal as an integral part of the modern life system. (Scott, 2025)

With the right approach, halal medical services have the potential to become one of the main pillars in the economic transformation of Islamic development in Indonesia. However, without a clear strategy and consistent implementation, this potential will only become a discourse without real realization.

## CONCLUSION

The economic transformation of Islamic development in the health sector through halal medical services is a clear indicator that the Islamic economy has moved beyond its traditional boundaries, which have been dominated by the financial sector. This development confirms that Islamic economics is not just an alternative system in the banking and financial fields, but a comprehensive paradigm that is able to respond to the needs of modern society more broadly, including in the health sector. In this context, halal medical services are present as a manifestation of integration between sharia values and contemporary health service practices that emphasize professionalism, efficiency, and service quality.

The concept of halal medical services offers an approach that not only focuses on the medical aspect but also integrates ethical and spiritual dimensions in the health service process. This is the main differentiator from conventional health systems, which tend to be oriented towards clinical and technical aspects. In the framework of Islamic economics, health services should not only aim to cure diseases, but also to maintain human dignity, provide inner peace, and ensure that every process carried out is in accordance with the principles of halal and thayyib. Thus, halal medical services can be seen as a form of innovation that combines modern medical needs with religious values that are the foundation of the life of the Muslim community.

However, the great potential of halal medical services in Indonesia has not been fully balanced with adequate system readiness. One of the main obstacles lies in the regulatory aspect, which is still partial and has not been comprehensively integrated into the national health system. Although the Halal Product Assurance Law has provided a legal basis for the development of the halal industry, its implementation in the health sector still faces various limitations. This shows that there is a gap between normative policies and the implementable reality on the ground. Without specific and operational technical regulations, the development of halal medical services risks running undirected and inconsistent.

In addition, limited human resources are a significant challenge that cannot be ignored. Medical personnel generally have strong competence in clinical aspects, but do not necessarily have an adequate understanding of Sharia principles in the context of health services. This condition creates a competency gap that can hinder the integration of Islamic values in daily medical practice. Therefore, systematic efforts are needed in the form of training, certification, and the development of an educational curriculum that is able to combine medical science with a balanced understanding of sharia.

On the other hand, the infrastructure aspect is also a determining factor in the successful implementation of halal medical services. The availability of supporting facilities, such as halal certification systems for pharmaceutical products, sharia-based operational standards, and supporting technology, is still limited. This shows that the development of this sector cannot be done partially, but rather requires a systemic approach that covers the entire value chain of health services, from drug production to patient services. Without adequate infrastructure support, the concept of halal medical services risks becoming just a symbolic label without a strong substance.

Despite facing various challenges, the opportunity for the development of halal medical services in Indonesia is still very large. With a predominantly Muslim population, Indonesia has a very promising domestic market. In addition, global trends show that the demand for halal products and services continues to increase, not only in Muslim countries but also in non-Muslim countries.

This opens up opportunities for Indonesia to develop the halal health sector as part of a national economic strategy oriented towards global competitiveness. From an economic perspective of Islamic development, halal medical services have a strategic role in creating sustainable welfare. Quality health services in accordance with Sharia principles not only improve people's quality of life but also contribute to increasing economic productivity. More than that, this sector also has the potential to create a broad multiplier effect, such as the development of the halal pharmaceutical industry, increased investment, and the creation of new jobs. Thus, halal medical services not only have religious value, but also significant economic value.

However, it should be emphasized that the development of halal medical services should not be stuck on a symbolic approach that only highlights the label of "sharia" without being followed by substantive implementation. There is a risk that this concept will only be used as a marketing strategy without any fundamental changes in the service system. If this happens, then public trust may decline, and the main goal of Islamic economic development will not be achieved. Therefore, a strict monitoring mechanism as well as continuous evaluation is needed to ensure that every aspect of the service is truly in accordance with Sharia principles.

Strategically, the next step that needs to be taken is not only limited to increasing the number of sharia hospitals, but also building a fully integrated halal healthcare ecosystem. This ecosystem must include various components, ranging from strong regulations, competent human resources, adequate infrastructure, to research and innovation support. Without strong integration between these components, the development of halal medical services will run in a fragmented manner and will not be able to achieve a significant scale.

In addition, the role of the government is crucial in encouraging the development of this sector. The government not only plays a role as a regulator, but also as a facilitator who is able to create an environment conducive to the growth of the halal industry. This can be done through comprehensive policy formulation, providing incentives for industry players, and strengthening cooperation with various parties, both at the national and international levels. Without a strong commitment from the government, the development of halal medical services will be difficult to develop optimally.

From the industrial side, business actors in the health sector also need to carry out a more serious transformation in adopting Sharia principles. This includes not only the operational aspect, but also the organizational culture and business orientation. Meanwhile, the public as service users also has an important role in encouraging demand for halal-based health services. Public awareness and preferences will be the main factors that determine the success of the development of this sector.

If viewed comparatively, Indonesia is currently still lagging behind several other countries that have previously developed the concept of halal medical services. This shows that without planned and coordinated strategic steps, Indonesia risks losing momentum in the global halal industry. On the contrary, if the existing potential can be utilized optimally, Indonesia has a great opportunity to become a center for halal health services at the regional and even global levels.

Ultimately, the economic transformation of Islamic development through halal medical services is not just a sectoral agenda, but is part of a broader effort to realize an economic system that is fair, sustainable, and oriented towards community welfare. With the right approach, this sector can become one of the main pillars in national economic development that is not only materially strong but also has a deep moral and spiritual dimension.

## REFERENCES

Elgharbawy, A. A. M., & Muhammad Yusri, E. I. (2023). A Bibliometric Analysis of Halal Cosmetics and Halal Pharmaceuticals. Halalsphere, 3(2), 44–51. https://doi.org/10.31436/hs.v3i2.76

Hakim, U. H., & Anggraeni, F. (2023). The Pharmaceutical Industry in Halal Product Studies: A Systematic Literature Review Approach. JIOSE: Journal of Indonesian Sharia Economics, 2(2), 171–190. https://doi.org/10.35878/jiose.v2i2.901

Hussaana, A., Azida, N., ... A. M.-I. J. of, & 2023, U. (2023). The role of halal labels in consumers' decision to choose medicines: an observational study in pharmacies in Unggal Saras Ungaran pharmacies. Indonesian Journal of Medical and Pharmaceutical Science, 2(2), 40–47. https://ijmps.id/index.php/ijmps/article/view/146

Mahadi, F., & Ab Talib, M. S. (2023). Logistics and Supply Chain Management in Halal Pharmaceutical Research: A Systematic Literature Review Using PRISMA. Journal of Halal Science and Technology, 2(1), 54–67. https://doi.org/10.59202/jhst.v2i1.668

Ms. Harjit Gill. (2024). Indonesia's Halal Policy Position for Medical Device Medical Technology (Industry Perspective). That is why we need to be vigilant, and we need to be vigilant.

Rahman, S. A., Afiq, M., Azmi, A., & Bakar, A. (2023). Halal Pharmaceuticals Research Trends and Coverage: A Systematic Literature Review. Malaysian Journal of Medicine and Health Sciences, 19(7), 83–84.

Wibowo, I. A. (2025). Transformatıon Of Halal Health Management: Examınıng Opportunıtıes, Challenges, Regulatıons, And Strategıes For Sharıa Hospıtals In Indonesıa Irawan. WAISYA: Journal of Hindu Economics, 4(2), 123–144.

Zunianto, A. A., Perwitasari, D. A., & Nurkhasanah. (2023). Halal Pharmaceutical Trend: A Bibliometric Analysis. Saudi Journal of Humanities and Social Sciences, 8(7), 203–208. https://doi.org/10.36348/sjhss.2023.v08i07.001

# CHAPTER 2
# PATHOPHYSIOLOGY OF MUSCULOSKELETAL PAIN: FROM ACUTE INJURY TO CHRONIC PAIN

[1]Meerab WASEEM
[2]Wafa MAJEED
[3]Kashif JILANI
[4]Ayesha
[5]Khadija ALMAS

[1]Department of Epidemiology and Public Health, University of Agriculture, Faisalabad, Pakistan, meerabwaseem271@gmail.com, ORCID ID: 0009-0009-3345-3456
[2]Department of Pharmacy, Faculty of Health and Pharmaceutical Sciences, University of Agriculture Faisalabad, Faisalabad 38000, Pakistan, wafa.majeed@uaf.edu.pk, ORCID ID: 0000-0001-6983-4474
[3]Department of Biochemistry, University of Agriculture Faisalabad, Faisalabad 38000, Pakistan, Kashif.jillani@uaf.edu.pk, ORCID ID: 0000-0002-1761-4100
[4]Institute of Physiology and Pharmacology, University of Agriculture Faisalabad, Faisalabad 38000, Pakistan, ayeshanazar117@gmail.com, ORCID ID: 0009-0006-1446-3980
[5]Department of Epidemiology and Public Health, University of Agriculture, Faisalabad, Pakistan, Khadijaalmas147@gmail.com, ORCID ID: 0009-0007-6155-3118

## INTRODUCTION

Musculoskeletal pain ranks as the leading factor which disables people across the world because more than 33% of the global population experiences musculoskeletal disorders which create major impacts on their life quality and work productivity and medical service demands. The body structures which include muscles and bones and joints and ligaments and tendons produce nociceptive pain which people call musculoskeletal pain that develops into either acute or chronic conditions based on its duration and the original causes of the pain.. Acute pain is generally protective, indicating this tissue has been damaged, while chronic pain reflects a maladaptive state in which complex neurophysiological changes occur long after the original injury (Puntillo et al., 2021).

Neuroplastic changes create essential conditions which enable chronic pain to develop. The continuous presence of nociceptive signals causes neural pathway modifications which result in permanent alterations in pain perception. The brain regions which control pain modulation through their cortical and limbic system functions develop into dysfunctional states which produce both ongoing pain and mental disruptions together with emotional disturbances. The development of chronic musculoskeletal pain results from multiple factors which transform acute mechanical damage and inflammatory responses into neural plastic changes that affect peripheral nerves and CNS pathways and social elements of the patient. Modern pain science shows that chronic pain exists as a separate condition because it involves modified neural processing which affects both the peripheral and central nervous systems.These changes are thought to include mechanisms of sensitization, neuroimmune interactions, and cortical reorganization (Basbaum et al., 2009).

Since poor acute pain management can result in long-term impairment, an understanding of these pathways is crucial for improving therapeutic results. This chapter unites molecular and cellular and systemic perspectives to deliver a complete explanation of this complex disorder which studies the progression from initial injury to permanent musculoskeletal discomfort (Tracey & Mantyh, 2007).

## 1. SENSORY INNERVATION OF SKIN AND BONE

Research shows that skin and bone possess different patterns for their sensory nerve supply to their tissues. The human skin receives sensory nerve fiber input from three types of fibers which include Type II Aß fibers and Type III Aδ fibers and Type IV C fibers. The skin contains three types of sensory nerve fibers which include Type II or Aß fibers and Type III or Aδ fibers and Type IV or C fibers. TrkA+ fibers which people call "peptide rich" fibers represent about 30% of all sensory fibers that exist in the skin. These fibers produce tropomyosin receptor kinase A (TrkA) and they emit calcitonin gene-related peptide (CGRP). The population contains "peptide poor" nerve fibers which lack TrkA expression (TrkA− fibers) to complete their composition. Adult bones, on the other hand, have little to no innervation from Aß or TrkA− C fibers and are primarily innervated by Aδ and TrkA+ C fibers (80%) (Mantyh, 2014).

Bone and joint innervation features nerve fibers which display various physical characteristics including their shape and density and their structural arrangement. The periosteum contains the highest density of sensory nerve fibers throughout all bone sections because Aδ and C-sensory nerve fibers form a fishnet pattern which allows them to sense bone distortion and mechanical damage. The sympathetic nerve fibers which usually connect with blood vessels show a corkscrew pattern when they innervate them (Ivanusic, 2017).

Sensory nerve fibers branch out with varicose ends in bone marrow, whereas they are linear in cortical bone. Like in cortical bone, sympathetic fibers in bone marrow spiral around the arteries (Web of Science, 2026).

**Table 1.** Features of Bone Innervation and Skin Innervation

| Feature | Bone innervation | Skin innervation |
|---|---|---|
| Tissue type | Deep somatic structure | Superficial structure |
| Primary nerve fibers | A-delta fibers, C fibers | A-beta, A-delta, C fibers |
| Localization | Poorly localized | Well localized |
| Receptors | Nociceptors | Nociceptors, Mechanoreceptors. |
| Clinical significance | Fractures cause severe pain due to periosteum | Immediate sharp pain. |

### 1.1 Neurooimmune Interactions

Both peripheral and central nervous system inflammation can be sustained by persistent harmful stimulation. The immune system and nervous system establish a feedback system which enables them to direct each other through their interactive dialogue. Non-neuronal cells like glial, epithelial, mast, and mesenchymal cells may be involved in this process. The activated cells produce pro-inflammatory substances which include PGE2 and TNF-α and IL-1β and granulocyte-macrophage colony-stimulating factor and NGF that affect nociceptors in their vicinity. The process generates antidromic action potentials which lead to neurogenic inflammation through the release of CGRP and SP that produce vascular permeability and enable immune cells to move through blood vessels (Torsney, 2019).

The body creates a unified system through the actions of neurons and glia and mesenchymal cells and immune cells which respond to dangerous stimuli. The body creates an immune response through this network which leads to increased tissue damage and inflammation and produces allodynia and hyperalgesia and modifies pain processing which could lead to chronic pain. The therapeutic targets for pain relief need to understand that immune–neuronal interaction functions as a two-way system.Indeed, research is now being done on novel treatments that target neurotrophin release and immune-cell activation or migration (Conaghan et al., 2019).

## 2. ANATOMY AND PHYSIOLOGY OF MUSCULOSKELETAL PAIN

Specialized sensory neurons called nociceptors which detect harmful stimuli including mechanical damage and thermal harm and chemical discomfort have extensive nerve supply throughout musculoskeletal tissues. A-delta and C fibers serve as the main nociceptors which transmit pain information at different speeds through their fast and slow signal transmission capabilities.Deep musculoskeletal structures, in contrast to cutaneous tissues, can cause diffuse, poorly localized pain because of variations in innervation density and receptor distribution (Puntillo et al., 2021).

Primary afferent neurons transmit nociceptive information from peripheral tissues to the spinal cord which forwards these signals to the cortex and thalamus for conscious pain perception. Depending on physiological and psychological variables, descending inhibitory and facilitatory pathways can either dampen or increase pain signals (Puntillo et al., 2021).

The main source of musculoskeletal pain comes from non-neuronal cells which work together with neuronal systems to produce their effects. The local microenvironment receives its composition from immune cells and glial cells (astrocytes and microglia) and fibroblasts which produce inflammatory mediators that include cytokines and chemokines and prostaglandins and growth factors. The central nervous system receives improved synaptic transmission through these mediators which also make nociceptors more sensitive. The development of acute pain and the continuation of chronic pain states require the complex neuroimmune system which develops through the interaction between neurological and immune systems. Nociceptors together with immune cells establish a two-way communication system which boosts inflammatory signaling to produce peripheral and central sensitization that results in long-lasting musculoskeletal pain (Su et al., 2022).

## 3. ACUTE INJURY AND INFLAMMATORY RESPONSE

Acute musculoskeletal injuries develop when people experience physical trauma or when their bodies receive excessive use or mechanical pressure which results in harm to their muscle and ligament and tendon and bone tissues. The body responds to this injury by starting an instant inflammatory reaction which functions as both a defensive system and a vital healing mechanism. The primary aim of inflammation is to remove damaged tissue, prevent further injury, and initiate repair. The inflammatory response is a series of biological processes that are triggered by acute musculoskeletal injuries. Pro-inflammatory mediators such prostaglandins, cytokines (like TNF-α and IL-1β), and bradykinin are released during this crucial tissue repair process. These drugs increase the experience of pain at the site of damage by sensitizing nociceptors (Cavanaugh et al., 2009). The body's inflammatory response leads to two changes; it makes blood vessels more accessible and it causes blood vessels to expand.

The body's healing process is affected by inflammation which develops into tissue damage and extended pain when it continues beyond its normal duration. Neurogenic inflammation extends the body's inflammatory response through neuropeptides which include substance P and calcitonin gene-related peptide (CGRP) (The Role of Neurogenic Inflammation in Fibromyalgia Pathophysiology, 2018).

The body normally handles inflammation through its established control mechanisms. The body continues to experience heightened pain because it fails to control this process which should have stopped after the initial pain period. The evaluation demonstrates that immediate medical attention for acute injuries serves as the primary strategy to prevent development of long-term health problems. The process of tissue damage occurs through biological events which start with inflammatory mediators and continue through the activation of neutrophils and macrophages and mast cells. Neutrophils become the first immune cells to reach the injury area because they help remove waste while producing proteolytic enzymes and reactive oxygen species. The macrophages function as growth factor providers who release vascular endothelial growth factor (VEGF) and transforming growth factor-beta (TGF-β) which activate inflammatory processes and support tissue repair. The processes which occur during healing become essential for recovery but their improper function leads to ongoing pain signals (Yohanes Firmansyah et al., 2024).

The immune cells active state maintains a continuous release of cytokines and chemokines which establishes a chronic inflammatory microenvironment. The ongoing state of inflammation decreases the pain threshold while maintaining the sensitivity of nociceptors. The situation leads to two outcomes in which normally non-painful stimuli become painful through allodynia and normally painful stimuli result in hyperalgesia which causes excessive pain responses. The condition of persistent peripheral inflammation together with its activation of spinal cord glial cells results in allastrocytes and microglia becoming active. The cells in pain pathways use their ability to release neuromodulators together with pro-inflammatory cytokines to enhance synaptic transmission. Neuroinflammation serves as the central element of inflammation which maintains persistent musculoskeletal pain by sustaining the transmission of signals from the body to the brain.

The body experiences structural tissue changes which include fibrosis and joint mechanics changes and improper tissue repair management because of continuous or persistent inflammatory damage. The changes will result in permanent functional disabilities which will extend the duration of nociceptive signals. The medical field considers immediate treatment for acute inflammation essential because it supports tissue healing and prevents chronic pain conditions from developing. The acute musculoskeletal injury treatment process requires medical professionals to concentrate on two areas which involve managing inflammation and facilitating tissue recovery. The medical field uses rest ice compression and elevation RICE together with nonsteroidal anti-inflammatory drugs NSAIDs to treat patients who need relief from inflammation and pain during this specific time (Jensen & Finnerup, 2014).

## 4. PERIPHERAL SENSITIZATION

The mechanism of peripheral sensitization leads to enhanced nociceptive neuron activity in the peripheral nervous system while reducing their pain detection capacity after tissue damage or inflammation. The process starts when primary nociceptor neurons become excessively active due to their interaction with inflammatory chemicals, which results in amplified pain signals even from small sensory triggers. The body produces chemical substances called prostaglandins, bradykinin, serotonin, histamine, and pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) which injured cells and immune system cells release after a body sustains an acute musculoskeletal injury. The drugs change ion channel function by binding to nociceptor terminal receptors which primarily affect sodium and calcium channels. The neuronal cells exhibit increased excitability due to this mechanism. The distinctive feature of peripheral sensitization includes the process in which chemical and thermal sensing TRP channels undergo modification. Inflammatory chemicals cause nociceptors to become more sensitive to mechanical and thermal stimuli by lowering their activation threshold for these channels. This adds to the clinical signs of hyperalgesia, a condition in which painful stimuli are interpreted as being more intense than usual (Caterina, 2000).

The phenomenon of spontaneous neuronal activity occurs when nociceptors activate without any external triggers due to peripheral sensitization. This abnormal activity pattern causes the injured area to experience more intense pain and ongoing discomfort. The body increases pain signaling through receptor and ion channel upregulation to enhance sensitivity (Gold & Gebhart, 2010).

The clinical symptom of peripheral sensitization manifests as primary hyperalgesia which occurs at the location of an injury. Patients may experience three different types of complaints which include increased soreness and throbbing pain and heightened reactions to pressure or movement. The acute phase of the condition uses localized hypersensitivity as a protective function which prevents movement while promoting tissue healing but when the condition becomes chronic it transforms into persistent pain. The process of neurogenic inflammation occurs when activated nociceptors discharge neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) which represent a critical element in peripheral sensitization. The neuropeptides cause nociceptors to become more sensitive to pain because they boost the inflammatory process which leads to vasodilation and raised vascular permeability and the movement of immune cells. Peripheral sensitization develops through a complex set of biochemical and cellular and molecular transformations which cause increased nociceptor activity. The condition exists as an essential mechanism which generates and sustains musculoskeletal pain in humans while linking acute injuries to their development into chronic pain conditions. The mechanism needs to be understood because it serves as the foundation for creating effective pain management treatments which will lead to better outcomes for patients (Pietro Emiliano Doneddu et al., 2023).

## 5. CENTRAL SENSITIZATION

Central sensitization causes enhanced neuronal excitability which affects the central nervous system and it functions as a primary mechanism that produces ongoing musculoskeletal pain. The body uses this mechanism to increase pain perception although there is no ongoing tissue damage.

The disease shows three main symptoms which include increased spinal and supraspinal neuron activity and decreased inhibitory control and enhanced synaptic transmission (Woolf, 2011).

The extension of receptive fields, which results in extensive pain outside of the initial lesion site, defines central sensitization through its characteristic symptoms. Chronic pain syndromes like fibromyalgia and persistent low back pain frequently exhibit this tendency. The brain circuitry changes lead to reduced activation thresholds which result in heightened pain perception (Apkarian et al., 2009).

By producing pro-inflammatory cytokines and regulating neuronal activity, glial cells including microglia and astrocytes play a critical role in central sensitization. These cells' activation sustains pain signaling in the central nervous system and adds to neuroinflammation (Mense, 2003).

The brainstem's descending modulatory circuits undergo extensive modifications during central sensitization. The pathways which begin in rostral ventromedial medulla RVM and periaqueductal gray PAG areas use their control mechanism to determine pain levels through their nociceptive transmission acceleration and deceleration functions. Chronic pain disorders typically bring about a transition which enhances pain perception while reducing the body's natural pain relief abilities (Ossipov et al., 2010).

The process of central sensitization gets strong influence from changes which occur in neurochemical systems. Neurons remain active for longer periods because of their reduced inhibitory neurotransmitter levels and their increased glutamate and substance P neurotransmitter levels. Microglia which operate in active state release brain-derived neurotrophic factor BDNF which creates new pain pathways through its function of sustaining long-term changes in neuronal activity and enhancing synaptic transmission (Coull et al., 2005).

Understanding central sensitization is essential for efficient pain treatment from a therapeutic standpoint. Treatments that only target peripheral tissues may not be effective for patients with major central mechanisms. Rather, treatments that target central nervous system activity, like cognitive-behavioral therapy, antidepressants, anticonvulsants, and neuromodulation approaches, are frequently more successful in lowering pain and enhancing function (Nijs et al., 2011).

Central sensitization develops through a combination of synaptic plasticity and neurochemical changes and inhibited brain function and brain structural changes. The acute-to-chronic transition of musculoskeletal pain requires mechanism-based methods for diagnosis and treatment according to this study which shows their essential role in pain management (Latremoliere & Woolf, 2009).

**Table 2.** Features of Peripheral Sensitization and Central Sensitization

| Feature | Peripheral Sensitization | Central Sensitization |
|---|---|---|
| Location | Injury site | Brain and Spinal cord |
| Cause | Inflammatory mediators | Repeated stimulation |
| Effect | Enhanced sensitivity of Nociceptor | Amplified pain signals |
| Clinical Indication | Localized hyperalgesia | Allodynia, widespread pain |

## 6. NEUROIMMUNE INTERACTIONS

The body experiences musculoskeletal pain because immune system and nervous system functions interact with each other. Neurons transmit neuropeptides to immune cells which activate their body functions while immune cells produce growth factors and cytokines which lead to increased pain sensitivity through nociceptor activation. The two-way communication system creates a feedback mechanism that results in extended periods of pain and inflammation (Frank et al., 2021).

Because they release mediators that improve nociceptive signaling, mast cells, macrophages, and T-cells are especially crucial in this process. Furthermore, by encouraging neuroinflammation and modifying synaptic function, microglial activation in the central nervous system adds to chronic pain (Grace et al., 2014).

Age, sex, and genetic predisposition are some of the factors that impact this neuroimmune crosstalk and can impact a person's vulnerability to chronic pain. Developing targeted therapeutics to modify immune responses and lessen pain requires an understanding of these interactions (Taylor et al., 2021).

Pro-inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) play a significant role in neuroimmune interaction. It has been demonstrated that these mediators, which are secreted by activated immune cells, directly affect nociceptive signaling by reducing the peripheral nociceptors' activation threshold. These cytokines reinforce persistent pain states in the central nervous system by improving synaptic transmission and long-term potentiation of pain pathways (Khan et al., 2017).

Chemokines and their receptors play a crucial role in controlling how neuroimmune cells interact with each other. The body increases its production of chemokines CCL2 and CXCL1 in response to tissue damage and inflammation which leads to immune cell movement towards the damaged region. Chemokine receptors present on neurons and glial cells create a mechanism for both systems to communicate which boosts nociceptive signaling and facilitates peripheral and central sensitization. The scientific community has started to recognize that glial cells function as active pain regulators instead of serving as simple supporting cells. Microglia activation leads to the release of various pro-inflammatory substances which make neurons more excited through their emission of cytokines and reactive oxygen species and neurotrophic factors. Astrocytes serve to maintain synaptic balance while they manage the levels of glutamate that exists outside synapses; however, when these cells experience deregulation, it leads to excitotoxicity and the continuation of pain signals (Xu et al., 2022).

The central nervous system's derangement of its inhibitory pathways leads to another mechanism which produces chronic musculoskeletal pain. The body usually prevents excessive nociceptive signals through the action of inhibitory neurotransmitters which include glycine and gamma-aminobutyric acid GABA. The neuroimmune activation process creates disinhibition of pain pathways together with increased pain perception because it blocks the body's inhibitory signaling mechanisms. Chronic pain disorders exist because their sufferers experience more excitement than their body can control. The central nervous system's failure to control its inhibitory pathways leads to persistent muscle and joint pain.

Nociceptive signals cannot reach excessive levels because glycine and gamma-aminobutyric acid (GABA) function as inhibitory neurotransmitters. Neuroimmune activation disrupts inhibitory signaling which leads to disinhibition of pain pathways and increased pain sensitivity. Chronic pain disorders exist because their sufferers experience more excitement than their body can control. Neuroimmune activation continues for long periods which leads to structural and functional changes in the central nervous system through neuroplasticity. The brain changes include new patterns of connections between brain regions which connect the limbic system and anterior cingulate cortex and prefrontal cortex to pain processing and emotional processing and cognitive processing. The clinical management of musculoskeletal pain is made more difficult by this rearrangement, which not only prolongs pain but also leads to related comorbidities like anxiety, depression, and cognitive decline (Mara et al., 2024).

## 7. NEUROPLASTICITY AND CORTICAL REORGANIZATION

Neuroplasticity describes the neural system's ability to modify its structure and function as a response to both traumatic experiences and everyday life events. The development of maladaptive neuroplastic changes results in the creation of stronger pain pathways which leads to increased severity of chronic pain symptoms. The changes consist of alterations which affect cortical representation and synaptic strength and neural connection patterns. Functional MRI studies have demonstrated that chronic pain patients develop brain region changes which affect pain processing systems that include insula and anterior cingulate cortex and prefrontal cortex brain areas. The emotional and cognitive factors which define pain experience develop from these changes which include anxiety and despair and pain catastrophizing (Seminowicz & Moayedi, 2017).

The correct medical interventions can reverse neuroplastic changes which scientists consider permanent. The brain treatment programs which use cognitive-behavioral therapy and neuromodulation techniques to restore healthy brain function receive this evidence. Chronic pain situations also impair the functional connections between brain networks.

The brain needs to communicate properly through the default mode network and salience network and executive control network to maintain its ability to handle and control pain signals. People with chronic pain disorders experience attention problems and memory deficits and emotional control difficulties which result from these network-level changes. New treatment strategies seek to encourage adaptive brain reconfiguration by utilizing the concepts of neuroplasticity. The programs which include graded motor imagery and mirror therapy and mindfulness-based stress reduction and focused physical rehabilitation aim to retrain brain circuits while restoring normal brain activity patterns. The methods which enhance positive neuroplastic changes will boost functional abilities while reducing pain intensity and supporting long-term recovery when used together with drug treatment and psychosocial therapy (Yang & Chang, 2019).

## 8. PSYCHOSOCIAL FACTORS IN PAIN CHRONIFICATION

You have access to information that has been collected until the month of October in the year 2023. Psychological and social factors serve as the main reasons which determine when people develop musculoskeletal pain and how long they will experience it. Central sensitization can be worsened through the combination of stress and anxiety and despair and unhealthy coping methods. The variables determine how a person experiences pain and their response to treatment. Environmental factors, along with social context, create a large impact on how people experience pain. The combination of work dissatisfaction and limited social support and cultural beliefs about pain and financial stressors can create conditions which intensify pain perception and block recovery. People who experience feelings of isolation and lack of support will experience higher rates of pain-related disabilities and emotional distress. People who have strong social support systems and good relationships will experience less stress and better coping abilities and higher treatment plan compliance, which will decrease their chances of developing chronic pain. The biopsychosocial paradigm explains how pain will develop from biological, psychological, and social elements which interact with each other.

Fear-avoidance behaviors will decrease exercise, which will lead to muscle deconditioning and increased pain sensitivity. Effective pain management needs the resolution of psychosocial factors. Researchers have found that cognitive-behavioral therapy and mindfulness-based stress reduction, along with patient education, help chronic musculoskeletal pain patients achieve better treatment results (Stilwell & Harman, 2019).

The existence of persistent pain becomes worse when people develop incorrect beliefs about pain which include thinking about worst-case scenarios and assuming that all movement will worsen their injuries. People who experience these cognitive tendencies will develop a pattern which includes inactivity and physical decline that leads to increased disability. The psychological treatment of these beliefs through dedicated mental health work enables doctors to help patients develop new pain management skills while better understanding their pain experience. The presence of chronic musculoskeletal pain links strongly with emotional problems which especially affect people with anxiety and depression. The disorders heighten pain symptoms by altering neurotransmitter functions and decreasing the body's pain thresholds. Patients with mood disorders and chronic pain experience more intense pain and poorer sleep and diminished quality of life. Mental health support should be part of pain management because it helps people with mood disorders who have chronic pain. The application of biological psychological and social assessment methods in chronic pain treatment enables healthcare providers to create customized treatment plans which enhance patient care. The best approach to treat chronic musculoskeletal pain and enhance long-term patient outcomes is increasingly acknowledged to be multidisciplinary care models that integrate medical, physical, and psychosocial therapy (Crofford, 2015).

## 9. TRANSITION FROM ACUTE TO CHRONIC PAIN

The transition from acute to chronic pain involves complex interactions between peripheral and cerebral processes. Continuous central nervous system activation occurs because of ongoing nociceptive signals from damaged tissues which leads to permanent changes in pain processing.

The process depends on three factors which include individual vulnerability, inflammation level, and injury severity. Genetic factors lead to pain chronification through their effects on neurotransmitter genes and ion channel genes and inflammatory mediator genes which determine pain sensitivity and recovery patterns. The environmental factors which include stress and lifestyle changes can change the operation of these systems. The risk of developing chronic pain increases when acute pain remains untreated. The prevention of permanent disabilities needs early treatment which stops inflammation and nociceptive pain and treats psychological factors. The process of acute pain turning into chronic pain occurs because low-grade inflammation continues after tissue damage has been repaired. The human body produces continuous chemokines and cytokines which sustain nociceptor activation because some individuals do not completely resolve their inflammatory conditions. This protracted inflammatory state reinforces chronic pain pathways by facilitating central sensitization and contributing to continuous peripheral input (Wall & Melzack's Textbook of Pain E-Book, 2026).

The development of chronic pain depends on how maladaptive changes in the peripheral nervous system progress through time. After an injury, damaged nerve fibers show a tendency to grow back incorrectly, which leads to ectopic firing and increased sensitivity. The changes that occur in the body create conditions which produce neuropathic symptoms in musculoskeletal pain disorders while they make the body transmit pain signals more effectively. Immediate and proper treatment of acute pain serves as the most effective method to decrease the chances that a person will develop chronic pain. The evidence shows that multidisciplinary approaches which combine medication with physical therapy and psychological support deliver better results than treatments which use only one method. These tactics seek to address the various mechanisms that contribute to the chronification of pain (Henschke et al., 2015).

**Table 3.** Transition from Acute to Chronic Pain

| Stage | Time Frame | Neural Mechanisms | Clinical Features | Key Factors |
|---|---|---|---|---|
| **Acute Injury** | 0-7 days | Activation of nociceptors (A-delta, C fibers) | Sharp, localized pain | Prostaglandins, bradykinin, histamine |
| **Inflammatory phase** | Days to weeks | Increased peripheral nerve excitability | Throbbing, aching pain | Cytokines (IL-1, TNF-α), substance |
| **Peripheral Sensitization** | Days to Weeks | Upregulation of nociceptor responsiveness | Hyperalgesia at affected area | Increased ion channel activity, inflammatory mediators |
| **Early Central Changes** | Weeks | Enhanced synaptic transmission in dorsal horn | Expanding pain area | NMDA receptor activation, glutamate |
| **Central Sensitization** | Weeks to Months | Neuronal hyperexcitability, reduced inhibition | Allodynia, pain spread beyond injury site | Glutamate, substance P, loss of inhibitory control |
| **Chronic Pain** | Greater than 3 months | Reorganization of pain pathways in CNS | Persistent, diffuse, disproportionate pain | Psychological factors, cortical reorganization |

## 10. CLINICAL IMPLICATIONS AND MANAGEMENT

The effective treatment of musculoskeletal pain through therapeutic methods needs complete understanding of the pain's underlying causes. Pain results from multiple mechanisms which require treatment approaches to include multiple treatment methods instead of using a single treatment method. Clinicians must use a mechanism-based approach to treatment design because they need to identify which nociceptive or neuropathic or centrally mediated mechanisms are active in the patient. Pharmacological management remains essential for treating musculoskeletal pain during the acute phase of treatment. Patients commonly use acetaminophen together with nonsteroidal anti-inflammatory medications (NSAIDs) to reduce their pain and swelling symptoms.

The effectiveness of antidepressants (which include serotonin-norepinephrine reuptake inhibitors) and anticonvulsants (which include gabapentinoids) in treating neuropathic and centrally mediated pain arises from their ability to target central pain pathways (Dworkin et al., 2007).

Patients with chronic musculoskeletal pain need both medication and additional treatment methods for their condition. Long-term opioid treatment exposes patients to three main dangers which include developing drug tolerance and becoming dependent on the medication and experiencing harmful reactions. The present medical guidelines recommend non-drug treatments as the first choice of therapy for patients while they restrict opioid prescription to cases which require it. Physical therapy and exercise-based therapies serve as fundamental treatment methods which enable patients to achieve their functional goals and experience pain relief. Targeted workouts help people improve their movement habits while they also build joint stability and muscle strength and flexibility. Exercise functions as a pain relief method because it improves central pain inhibition while the body produces natural painkilling substances. The process of managing pain effectively requires both self-management methods and educational materials. Patients need to learn about pain because their understanding of central sensitization will decrease their fear-avoidance habits while they practice active coping skills. In people with long-term musculoskeletal disorders, pain neuroscience education has been demonstrated to lessen pain intensity and enhance functional outcomes (Louw et al., 2016).

The psychological treatment of chronic pain patients requires psychological therapy as a critical necessity. People who undergo cognitive-behavioral therapy (CBT) learn to control their emotional pain while developing their ability to handle difficult situations through active changes of their negative pain-related thought patterns and their harmful behavior patterns. Mindfulness-based stress reduction together with other techniques has demonstrated effectiveness in reducing pain perception while enhancing life quality. The best outcomes for pain management arise from interdisciplinary programs which combine physical and psychological and medicinal treatments.

The programs deal with the complex nature of musculoskeletal pain by providing complete symptom relief together with quality of life improvements and functional rehabilitation. The treatment of musculoskeletal pain requires a patient-specific approach which needs to treat both peripheral and central pain mechanisms. The combination of pharmaceutical and non-pharmacological treatments together with patient education and psychological support provides the most effective method for reducing pain and preventing chronicity (Del Giovane et al., 2019).

New research shows that lifestyle factors play an essential part in treating patients who have musculoskeletal pain conditions. People who lead sedentary lives and experience sleep problems while eating unhealthy food will face two challenges because their pain perception will increase and their body healing process will become slower. People who have sleep problems will experience two effects because their body will develop higher pain sensitivity and their body will lose its ability to handle pain. Clinicians need to assess sleep hygiene functions and balanced nutrition functions and regular physical activity functions as part of complete pain management treatment. The long-lasting impact of musculoskeletal disorders depends on how inflammation and metabolic health processes operate in the body. Persistent discomfort arises from low-grade systemic inflammation which happens to people who have obesity and metabolic disorders. Weight management techniques which include dietary changes and exercise can decrease inflammatory markers while reducing joint load which leads to pain relief and improved function in patients with osteoarthritis. Active rehabilitation procedures become more effective when combined with manual therapy methods which include joint mobilization and manipulation and soft tissue therapy as they help patients gain mobility while providing temporary relief from pain. The early treatment stage benefits from passive therapies because they help patients start their physical activities and functional tasks although these therapies lack effectiveness on their own as treatment methods (Kirsch Micheletti et al., 2019).

## CONCLUSION

Musculoskeletal pain represents a complex disorder which develops through interactions between three types of factors: neurological factors and psychological factors and biological factors. The central nervous system and peripheral tissues undergo fundamental changes which cause the transition process from acute injury to chronic pain to take place after a specific time period. Pain experience develops through mechanisms which operate through inflammation and peripheral sensitization and central sensitization. The transition to chronic pain develops through multiple factors which include genetic predisposition and psychological state and environmental effects and the effectiveness of early pain management. Chronic pain exists as a condition which maintains itself through continuous nociceptive signals and neuroplastic changes and malfunctioning pain control systems.

It is crucial to consider chronic musculoskeletal pain from a biopsychosocial perspective, acknowledging that social, cognitive, and emotional aspects play a significant role in the pain experience. Effective therapy necessitates addressing these aspects, which calls for a move away from strictly biological models and toward more all-encompassing care approaches. The understanding of musculoskeletal pain mechanisms has advanced through pain research progress, which resulted in improved treatment methods that directly target pain conditions. The clinical application of this information remains challenging because of the need to establish multidisciplinary treatment access and to implement personalized treatment plans. Future research should focus on discovering pain biomarkers and improving diagnostic accuracy and developing patient-specific treatment approaches. The assessment and management of pain will benefit from advanced technologies, which include neuroimaging and digital health tools. The effective treatment of acute pain conditions and chronic pain development depends on understanding the biological mechanisms that cause musculoskeletal pain. The healthcare system can more effectively address pain challenges and reduce its social and individual impact through their method that combines different fields of study with a focus on pain mechanisms (Pozek et al., 2016).

## REFERENCES

Apkarian, A. V., Baliki, M. N., & Geha, P. Y. (2009). Towards a theory of chronic pain. Progress in Neurobiology, 87(2), 81–97. https://doi.org/10.1016/j.pneurobio.2008.09.018

Basbaum, A. I., Bautista, D. M., Scherrer, G., & Julius, D. (2009). Cellular and Molecular Mechanisms of Pain. Cell, 139(2), 267–284. https://doi.org/10.1016/j.cell.2009.09.028

Caterina, M. J. (2000). Impaired Nociception and Pain Sensation in Mice Lacking the Capsaicin Receptor. Science, 288(5464), 306–313. https://doi.org/10.1126/science.288.5464.306

Cavanaugh, D. J., Lee, H., Lo, L., Shields, S. D., Zylka, M. J., Basbaum, A. I., & Anderson, D. J. (2009). Distinct subsets of unmyelinated primary sensory fibers mediate behavioral responses to noxious thermal and mechanical stimuli. Proceedings of the National Academy of Sciences, 106(22), 9075–9080. https://doi.org/10.1073/pnas.0901507106

Conaghan, P. G., Cook, A. D., Hamilton, J. A., & Tak, P. P. (2019). Therapeutic options for targeting inflammatory osteoarthritis pain. Nature Reviews Rheumatology, 15(6), 355–363. https://doi.org/10.1038/s41584-019-0221-y

Coull, J. A. M., Beggs, S., Boudreau, D., Boivin, D., Tsuda, M., Inoue, K., Gravel, C., Salter, M. W., & De Koninck, Y. (2005). BDNF from microglia causes the shift in neuronal anion gradient underlying neuropathic pain. Nature, 438(7070), 1017–1021.

Crofford, L. J. (2015). Psychological aspects of chronic musculoskeletal pain. Best Practice & Research. Clinical Rheumatology, 29(1), 147–155. https://doi.org/10.1016/j.berh.2015.04.027

D. A., & Moayedi, M. (2017). The Dorsolateral Prefrontal Cortex in Acute and Chronic Pain. The Journal of Pain, 18(9), 1027–1035. https://doi.org/10.1016/j.jpain.2017.03.008

Del Giovane, C., Cortese, S., & Cipriani, A. (2019). Combining Pharmacological and NonpharmacologicalInterventionsinNetworkMeta-analysisinPsychiatry. JAMA Psychiatry, 76(8), 867.

Dworkin, R. H., O'Connor, A. B., Backonja, M., Farrar, J. T., Finnerup, N. B., Jensen, T. S., Kalso, E. A., Loeser, J. D., Miaskowski, C., Nurmikko, T. J., Portenoy, R. K., Rice, A. S. C., Stacey, B. R., Treede, R.-D., Turk, D. C., & Wallace, M. S. (2007). Pharmacologic management of neuropathicpain:Evidence-basedrecommendations. Pain, 132(3),237–251. https://doi.org/10.1016/j.pain.2007.08.033

Frank, Indra, Geraets, J., Foreman, Y. D., Ronald, Kroon, A. A., Carla, Thomas, Dagnelie, P. C., Dongen, van, Simone, Tos T. J. M. Berendschot, Jan, Carroll, Marleen, Wesselius, A., Koster, A., Schaper, N. C., Schram, M. T., & Seb Köhler. (2021). Association of Retinal Nerve Fiber Layer Thickness, an Index of Neurodegeneration, With Depressive Symptoms Over Time. JAMA NetworkOpen, 4(11),e2134753–e2134753. https://doi.org/10.1001/jamanetworkopen.2021.34753

Gold, M. S., & Gebhart, G. F. (2010). Nociceptor sensitization in pain pathogenesis. Nature Medicine, 16(11), 1248–1257. https://doi.org/10.1038/nm.2235

Grace, P. M., Hutchinson, M. R., Maier, S. F., & Watkins, L. R. (2014). Pathological pain and the neuroimmuneinterface. NatureReviews.Immunology, 14(4),217–231.

Henschke, N., Kamper, S. J., & Maher, C. G. (2015). The Epidemiology and Economic ConsequencesofPain. MayoClinicProceedings, 90(1),139–147. https://doi.org/10.1016/j.mayocp.2014.09.010

Ivanusic, J. J. (2017). Molecular Mechanisms That Contribute to Bone Marrow Pain. Frontiers in Neurology, 8.

Jensen, T. S., & Finnerup, N. B. (2014). Allodynia and hyperalgesia in neuropathic pain: clinical manifestations and mechanisms. The Lancet. Neurology, 13(9), 924–935. https://doi.org/10.1016/S1474-4422(14)70102-4

Khan, J., Noboru, N., Young, A., & Thomas, D. (2017). Pro and anti-inflammatory cytokine levels (TNF-α, IL-1β, IL-6 and IL-10) in rat model of neuroma. Pathophysiology, 24(3), 155–159. https://doi.org/10.1016/j.pathophys.2017.04.001

Kirsch Micheletti, J., Bláfoss, R., Sundstrup, E., Bay, H., Pastre, C. M., & Andersen, L. L. (2019). Association between lifestyle and

musculoskeletal pain: cross-sectional study among 10,000 adults from the general working population. BMC Musculoskeletal Disorders, 20(1). https://doi.org/10.1186/s12891-019-3002-5

Latremoliere, A., & Woolf, C. J. (2009). Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity. The Journal of Pain, 10(9), 895–926. https://doi.org/10.1016/j.jpain.2009.06.012

Louw, A., Zimney, K., Puentedura, E. J., & Diener, I. (2016). The Efficacy of Pain Neuroscience Education on Musculoskeletal Pain: A Systematic Review of the Literature. Physiotherapy Theory and Practice, 32(5), 332–355. https://doi.org/10.1080/09593985.2016.1194646

Mantyh, P. W. (2014). The neurobiology of skeletal pain. European Journal of Neuroscience, 39(3), 508–519. https://doi.org/10.1111/ejn.12462

Mara, S., Ligia Gabriela Tataranu, Kamel, A., Serban Turliuc, Radu Eugen Rizea, & Anica Dricu. (2024). Glioblastoma and Immune Checkpoint Inhibitors: A Glance at Available Treatment Options and Future Directions. International Journal of Molecular Sciences, 25(19), 10765–10765. https://doi.org/10.3390/ijms251910765

Mense, S. (2003). The pathogenesis of muscle pain. Current Pain and Headache Reports, 7(6), 419–425. https://doi.org/10.1007/s11916-003-0057-6

Nijs, J., Paul van Wilgen, C., Van Oosterwijck, J., van Ittersum, M., & Meeus, M. (2011). How to explain central sensitization to patients with "unexplained" chronic musculoskeletal pain: Practice guidelines. Manual Therapy, 16(5), 413–418.

Ossipov, M. H., Dussor, G. O., & Porreca, F. (2010). Central modulation of pain. Journal of Clinical Investigation, 120(11), 3779–3787. https://doi.org/10.1172/jci43766

Perrot, S. (2015). Osteoarthritis pain. Best Practice & Research Clinical Rheumatology, 29(1), 90–97. https://doi.org/10.1016/j.berh.2015.04.017

Pietro Emiliano Doneddu, Umberto Pensato, Iorfida, A., Alberti, C., Nobile-Orazio, E., Fabbri, A., & Voza, A. (2023). Neuropathic Pain in the Emergency Setting: Diagnosis and Management. Journal of Clinical Medicine, 12(18), 6028–6028. https://doi.org/10.3390/jcm12186028

Pozek, J.-P. J., Beausang, D., Baratta, J. L., & Viscusi, E. R. (2016). The Acute to Chronic Pain Transition. MedicalClinicsofNorthAmerica, 100(1),17–30. https://doi.org/10.1016/j.mcna.2015.08.005

Puntillo, F., Giglio, M., Paladini, A., Perchiazzi, G., Viswanath, O., Urits, I., Sabbà, C., Varrassi, G., & Brienza, N. (2021). Pathophysiology of musculoskeletal pain: a narrative review. Therapeutic Advances in Musculoskeletal Disease, 13(13), 1759720X2199506. https://doi.org/10.1177/1759720x21995067

Puntillo, F., Giglio, M., Paladini, A., Perchiazzi, G., Viswanath, O., Urits, I., Sabbà, C., Varrassi, G., & Brienza, N. (2021). Pathophysiology of musculoskeletal pain: a narrative review. Therapeutic Advances in Musculoskeletal Disease, 13(13), 1759720X2199506.

Puntillo, F., Giglio, M., Paladini, A., Perchiazzi, G., Viswanath, O., Urits, I., Sabbà, C., Varrassi, G., & Brienza, N. (2021). Pathophysiology of musculoskeletal pain: a narrative review. Therapeutic Advances in Musculoskeletal Disease, 13(13), 1759720X2199506. https://doi.org/10.1177/1759720x21995067,

Stilwell, P., & Harman, K. (2019). An enactive approach to pain: beyond the biopsychosocial model. PhenomenologyandtheCognitiveSciences, 18(4),637–665. https://doi.org/10.1007/s11097-019-09624-7

Su, P.-Y. P., Zhang, L., He, L., Zhao, N., & Guan, Z. (2022). The Role of Neuro-Immune Interactions in Chronic Pain: Implications for Clinical Practice. Journal of Pain Research, Volume 15, 2223–2248.

Taylor, S.-S., Noor, N., Urits, I., Paladini, A., Sadhu, M. S., Gibb, C., Carlson, T., Myrcik, D., Varrassi, G., & Viswanath, O. (2021). Complex Regional Pain Syndrome: A Comprehensive Review. Pain and Therapy, 10(2), 875–892. https://doi.org/10.1007/s40122-021-00279-4

The Role of Neurogenic Inflammation in Fibromyalgia Pathophysiology. (2018, July 11). Rheumatology Advisor. https://www.rheumatologyadvisor.com/features/the-role-of-neurogenic-inflammation-in-fibromyalgia-pathophysiology/?utm_source=chatgpt.com

Torsney, C. (2019). Inflammatory pain neural plasticity. Current Opinion in Physiology, 11, 51–57. https://doi.org/10.1016/j.cophys.2019.06.001

Tracey, I., & Mantyh, P. W. (2007). The cerebral signature for pain perception and its modulation. Neuron, 55(3), 377–391. https://doi.org/10.1016/j.neuron.2007.07.012

Wall & Melzack's Textbook of Pain E-Book. (2026). Google Books. https://books.google.com.pk/books?hl=en&lr=&id=ok0_jIJ0w_wC&oi=fnd&pg=PP1&dq=(McMahon+et+al.

Web of Science. (2026). Webofscience.com. https://www.webofscience.com/wos/woscc/full-record/WOS:000468974200007?&SID=EUW1ED0C15MjoyoNpyqIsJtI7UZ9o

Woolf, C. J. (2011). Central sensitization: Implications for the diagnosis and treatment of pain. Pain, 152(3), S2–S15.

Xu, J., Wan, R., Xu, W., Ma, Z., Cheng, X., Yang, R., & Yin, X. (2022). Colored Radiative Cooling Coatings Using Phosphor Dyes. SSRN Electronic Journal. https://doi.org/10.2139/ssrn.4124069

Yang, S., & Chang, M. C. (2019). Chronic Pain: Structural and Functional Changes in Brain Structures and Associated Negative Affective States. International Journal of Molecular Sciences, 20(13), 3130. https://doi.org/10.3390/ijms20133130

Yohanes Firmansyah, Veronika Maria Sidharta, Wijaya, L., & Sukmawati Tansil Tan. (2024). Unraveling the Significance of Growth Factors (TGF-β, PDGF, KGF, FGF, Pro Collagen, VEGF) in the Dynamic of Wound Healing. Asian Journal of Medicine and Health, 22(3), 49–61. https://doi.org/10.9734/ajmah/2024/v22i3992

# CHAPTER 3
# DESIGN AND DEVELOPMENT OF FUNCTIONAL PLANT-BASED SUPPLEMENTS FROM *ASHITABA (ANGELICA KEISKEI)*: INTEGRATED EXTRACTION, PROCESSING, AND EFFERVESCENT FORMULATION APPROACH

[1]Arie Febrianto MULYADI

[1]Department of Agricultural Industrial Technology, Faculty of Agricultural Technology, Universitas Brawijaya, Indonesia, arie_febrianto@ub.ac.id, ORCID ID: 0000-0002-7193-7904

## INTRODUCTION

The global demand for plant-based functional supplements has increased significantly in recent years, driven by growing consumer awareness of the relationship between diet, health, and disease prevention. Functional supplements derived from botanical sources are increasingly preferred due to their perceived safety, bioactivity, and sustainability compared to synthetic compounds. This trend is particularly evident in the development of herbal-based nutraceuticals that offer antioxidant, anti-inflammatory, and therapeutic properties (Shahidi, 2012; Granato et al., 2020).

Among various bioactive-rich plants, Ashitaba (Angelica keiskei) has attracted considerable attention due to its unique phytochemical composition and wide range of pharmacological benefits. Native to Japan but increasingly cultivated in tropical regions, including Indonesia, ashitaba is known for its high content of chalcones, flavonoids, vitamins, and minerals. These compounds have been reported to exhibit strong antioxidant, anti-inflammatory, antimicrobial, and anticancer activities, making ashitaba a promising candidate for functional food and supplement applications (Zhang et al., 2019; Baba et al., 2007).

Chalcones, particularly xanthoangelol and 4-hydroxyderricin, are the most distinctive bioactive compounds in ashitaba. These compounds have demonstrated significant biological activities, including inhibition of oxidative stress and modulation of metabolic pathways associated with chronic diseases (Baba et al., 2007). However, the effectiveness of these bioactive compounds in functional applications is highly dependent on processing conditions, especially during extraction and formulation stages. Improper processing may lead to degradation or loss of bioactivity, thereby reducing the functional value of the final product (Dai & Mumper, 2010).

Extraction is a critical step in the valorization of plant-based materials, as it determines the yield, composition, and quality of the resulting extract. Conventional extraction methods such as maceration and Soxhlet extraction are widely used but often suffer from limitations including long processing time, high solvent consumption, and potential degradation of thermolabile compounds.

In contrast, emerging techniques such as Ultrasonic-Assisted Extraction (UAE) have been shown to significantly enhance extraction efficiency through acoustic cavitation, which disrupts plant cell walls and facilitates mass transfer (Chemat et al., 2017). UAE offers several advantages, including reduced extraction time, lower energy consumption, and improved preservation of bioactive compounds, making it highly suitable for extracting sensitive phytochemicals such as flavonoids and phenolics (Vilkhu et al., 2008).

Despite advances in extraction technologies, the transformation of plant extracts into stable and consumer-friendly dosage forms remains a major challenge. Traditional consumption methods of herbal materials, such as decoctions or infusions, are often inconvenient and lack dosage standardization. Therefore, the development of modern delivery systems, such as encapsulated supplements and effervescent formulations, is essential to enhance usability, stability, and bioavailability (Saha et al., 2020).

Effervescent formulations, in particular, have gained increasing attention as an innovative delivery system for functional ingredients. These formulations typically consist of a combination of acid (e.g., citric acid, tartaric acid) and base (e.g., sodium bicarbonate) components that react in the presence of water to produce carbon dioxide gas. The resulting effervescence enhances dissolution, improves taste masking, and facilitates rapid absorption of active compounds (Rowe et al., 2009). Moreover, effervescent systems are particularly advantageous for plant extracts with strong or unpleasant flavors, as they improve sensory acceptability while maintaining functional properties.

However, the formulation of effervescent products from plant extracts presents several technical challenges. These include moisture sensitivity, stability of bioactive compounds, flowability of granules, and optimization of acid-base ratios. The hygroscopic nature of plant extracts can adversely affect the physical properties of the formulation, while improper formulation design may compromise both product stability and functional efficacy (Aulton & Taylor, 2018). Therefore, a systematic approach that integrates extraction optimization with formulation design is required to develop high-quality functional supplements. In addition to formulation challenges, there is a growing need to consider industrial scalability and process integration.

Most existing studies focus on either extraction or formulation independently, with limited attention to the integration of upstream and downstream processes within an agroindustrial framework. Such integration is crucial to ensure consistency in product quality, process efficiency, and economic feasibility, particularly for large-scale production of plant-based supplements (Putnik et al., 2018).

Given these considerations, this chapter aims to present a comprehensive approach to the design and development of plant-based functional supplements using ashitaba as a model system. The chapter integrates extraction technology, particularly Ultrasonic-Assisted Extraction, with downstream formulation into capsule and effervescent dosage forms. Emphasis is placed on the relationship between process parameters and product quality, as well as the challenges and opportunities associated with industrial application. By bridging the gap between extraction and formulation, this work contributes to the development of an integrated agroindustrial system for producing high-value functional supplements.

## 1. BIOACTIVE COMPOUNDS AND FUNCTIONAL POTENTIAL OF ASHITABA

### 1.1 Bioactive Composition of Ashitaba

Ashitaba (Angelica keiskei) is widely recognized as a functional plant due to its rich composition of bioactive compounds, particularly chalcones, flavonoids, and phenolic antioxidants. These compounds are responsible for the plant's distinctive pharmacological properties and its growing application in functional food and nutraceutical industries.

Among these, chalcones are considered the most characteristic and biologically active constituents of ashitaba. The dominant chalcones identified include xanthoangelol and 4-hydroxyderricin, which have been reported to exhibit strong antioxidant and anti-inflammatory activities. These compounds play a crucial role in modulating oxidative stress and inhibiting inflammatory pathways, making them highly relevant for chronic disease prevention (Baba et al., 2007; Zhang et al., 2019).

In addition to chalcones, ashitaba contains significant levels of flavonoids, a class of polyphenolic compounds known for their ability to scavenge free radicals and enhance cellular defense mechanisms. Flavonoids contribute to the stabilization of reactive oxygen species (ROS) and are closely associated with the overall antioxidant capacity of plant extracts (Dai & Mumper, 2010). The presence of these compounds in ashitaba extract has been confirmed in experimental studies, where higher flavonoid content correlated with increased antioxidant activity, particularly under optimized extraction conditions .

Furthermore, total phenolic compounds represent another important group of bioactives in ashitaba. These compounds are known to act as primary antioxidants by donating hydrogen atoms or electrons to neutralize free radicals. The effectiveness of phenolic compounds is often reflected in DPPH radical scavenging assays, which are commonly used to evaluate antioxidant activity. In the case of ashitaba leaf extract obtained through Ultrasonic-Assisted Extraction (UAE), strong antioxidant activity was observed, with $IC_{50}$ values reaching approximately 45 ppm under optimal conditions.

## 1.2 Antioxidant and Anti-Inflammatory Properties

The functional potential of ashitaba is largely attributed to its antioxidant and anti-inflammatory properties, which are closely linked to its bioactive composition. Oxidative stress, caused by an imbalance between free radicals and antioxidant defenses, is a major contributor to the development of chronic diseases such as cardiovascular disorders, diabetes, and cancer. Natural antioxidants from plant sources have been widely studied for their ability to mitigate these effects (Shahidi, 2012).

Chalcones and flavonoids in ashitaba act as potent antioxidants by:

- Scavenging free radicals
- Inhibiting lipid peroxidation
- Enhancing endogenous antioxidant systems

In particular, xanthoangelol has been reported to inhibit the production of pro-inflammatory mediators and reduce oxidative damage at the cellular level (Zhang et al., 2019). These findings highlight the dual role of ashitaba compounds as both antioxidants and anti-inflammatory agents.

Experimental results from ashitaba extract also demonstrate that antioxidant activity is highly dependent on processing conditions. Optimized UAE conditions (moderate temperature and short extraction time) were shown to preserve bioactive compounds effectively, resulting in superior antioxidant performance . This reinforces the importance of controlled processing in maintaining the functional integrity of plant-derived compounds.

### 1.3 Stability and Functional Retention in Processed Products

Despite the strong bioactivity of ashitaba compounds, their stability during processing remains a critical concern. Phenolic compounds and flavonoids are generally sensitive to:

- Heat
- Oxygen exposure
- pH changes

During downstream processing, such as drying and formulation, partial degradation of these compounds may occur, leading to reduced functional activity (Chemat et al., 2017).

This phenomenon is also evident in effervescent formulations of ashitaba extract, where antioxidant activity tends to decrease compared to the crude extract. The reduction is primarily attributed to:

- Dilution effects
- Interaction with excipients
- Exposure to processing conditions

However, despite this reduction, the effervescent product still retains measurable antioxidant activity, indicating that the formulation process can preserve a significant portion of bioactive functionality.

### 1.4 Potential of Ashitaba in Effervescent Delivery Systems

Effervescent dosage forms offer a promising approach for delivering ashitaba bioactive compounds in a more stable, palatable, and bioavailable form. The integration of ashitaba extract into effervescent granules provides several functional advantages. First, the effervescent system enhances solubility and dispersion of bioactive compounds.

The reaction between organic acids (e.g., citric acid and tartaric acid) and sodium bicarbonate produces carbon dioxide, which facilitates rapid dissolution and improves the distribution of active compounds in aqueous media (Rowe et al., 2009).

Second, effervescent formulations improve sensory acceptability, particularly for plant extracts that may have a bitter or astringent taste. The addition of sweeteners and flavor-modifying agents, combined with the effervescence effect, can effectively mask undesirable sensory attributes, making the product more acceptable to consumers.

Third, the slightly acidic pH (typically around 4–5) of effervescent solutions can help maintain the stability of certain phenolic compounds and enhance antioxidant activity. In the case of ashitaba effervescent formulations, pH values in this range were observed, which are favorable for preserving functional properties .

Finally, effervescent systems provide a convenient and user-friendly dosage form, allowing for accurate dosing, rapid preparation, and improved compliance compared to traditional herbal preparations. These advantages make effervescent formulations particularly suitable for the commercialization of plant-based functional supplements.

### 1.5 Summary of Functional Potential

Overall, the combination of rich bioactive composition and versatile formulation potential positions ashitaba as a highly promising raw material for functional supplement development. The presence of chalcones, flavonoids, and phenolic compounds provides strong antioxidant and anti-inflammatory properties, while advanced processing techniques such as UAE and effervescent formulation enable the efficient delivery of these compounds in practical applications.

## 2. EXTRACTION TECHNOLOGIES

### 2.1 Ultrasonic-Assisted Extraction (UAE) Method

Extraction is a critical stage in the valorization of plant-based materials, as it determines the yield, composition, and functional quality of bioactive compounds.

In recent years, Ultrasonic-Assisted Extraction (UAE) has emerged as an efficient and sustainable alternative to conventional extraction techniques. UAE utilizes high-frequency ultrasonic waves (typically above 20 kHz) to induce acoustic cavitation, a phenomenon involving the formation, growth, and implosive collapse of microbubbles in a liquid medium. This process generates localized high temperatures and pressures, leading to the disruption of plant cell walls and enhanced mass transfer between the solvent and plant matrix (Chemat et al., 2017; Vilkhu et al., 2008).

Compared to conventional methods such as maceration or Soxhlet extraction, UAE offers several advantages, including shorter extraction time, reduced solvent consumption, and improved preservation of thermolabile compounds. These characteristics are particularly important for extracting bioactive compounds from Ashitaba (Angelica keiskei), which are sensitive to prolonged heat exposure and oxidative degradation. The application of UAE has been widely reported to improve the extraction efficiency of phenolic and flavonoid compounds, which are responsible for antioxidant activity in plant extracts (Dai & Mumper, 2010).

In this study, UAE was applied to extract bioactive compounds from dried ashitaba leaves. The use of ultrasonic energy facilitated the release of intracellular compounds, thereby enhancing extraction efficiency under relatively mild conditions. This approach aligns with the principles of green extraction, which emphasize energy efficiency, reduced solvent use, and improved product quality (Chemat et al., 2017).

## 2.2 Key Extraction Parameters

The efficiency of UAE is strongly influenced by several process parameters, particularly temperature, extraction time, and solvent type. These variables determine the balance between mass transfer enhancement and the stability of bioactive compounds.

### 2.2.1 Temperature

Temperature plays a dual role in extraction processes. On one hand, increasing temperature can enhance solubility and diffusion rates, thereby improving extraction efficiency.

On the other hand, excessive temperature may lead to the degradation of thermolabile compounds such as phenolics and flavonoids (Dai & Mumper, 2010).

In the case of ashitaba extraction using UAE, the temperature range investigated was 30°C to 45°C. Experimental results indicated that temperature did not significantly affect extraction yield within this range. However, antioxidant activity was highly sensitive to temperature variations, with optimal performance observed at moderate temperature (35°C) .

This finding suggests that moderate temperature conditions are sufficient to facilitate effective cavitation and mass transfer while minimizing thermal degradation. From an industrial perspective, operating at lower temperatures is advantageous as it reduces energy consumption and preserves product quality.

### 2.2.2 Extraction Time

Extraction time is another critical parameter that influences the efficiency of UAE. In general, longer extraction times allow more extensive diffusion of solutes into the solvent. However, excessive exposure to ultrasonic energy may lead to the degradation of sensitive compounds due to prolonged cavitation effects (Vilkhu et al., 2008).

In this study, extraction times of 20, 25, and 30 minutes were evaluated. The results showed that extraction time did not significantly affect yield, indicating that equilibrium between the plant matrix and solvent was reached relatively quickly. The optimal condition was identified at 20 minutes, which provided the highest antioxidant activity and efficient extraction performance .

This outcome highlights one of the key advantages of UAE: the ability to achieve high extraction efficiency within a short processing time. Shorter extraction times not only improve process efficiency but also reduce the risk of compound degradation and operational costs.

### 2.2.3 Solvent Selection

The choice of solvent is a fundamental factor in determining the selectivity and efficiency of extraction. Solvents with appropriate polarity are required to effectively dissolve target bioactive compounds.

For phenolic and flavonoid compounds, polar solvents such as ethanol are commonly used due to their compatibility with both hydrophilic and moderately lipophilic compounds (Dai & Mumper, 2010).

In this study, 96% ethanol was used as the extraction solvent with a solid-to-solvent ratio of 1:10. Ethanol offers several advantages, including:

- High extraction efficiency for phenolic compounds
- Low toxicity and food-grade safety
- Ease of removal during downstream processing

The use of ethanol also aligns with regulatory requirements for food and pharmaceutical applications, making it suitable for the production of functional supplements. Furthermore, ethanol enhances cavitation efficiency in UAE by improving solvent penetration into plant tissues.

## 2.3 Extraction Yield and Extract Quality

The performance of the extraction process can be evaluated based on yield and extract quality, including antioxidant activity and bioactive compound content.

### 2.3.1 Extraction Yield

The extraction yield obtained in this study ranged from approximately 5.33% to 7.67%, with the highest yield observed at 35°C for 20 minutes. Statistical analysis indicated that neither temperature nor extraction time had a significant effect on yield within the tested range .

This suggests that the extraction system had reached a stable equilibrium condition, where further increases in temperature or time did not significantly enhance solute recovery. Such behavior is typical in UAE processes, where cavitation rapidly disrupts cell structures and facilitates the release of intracellular compounds.

### 2.3.2 Antioxidant Activity and Bioactive Quality

While yield is an important parameter, extract quality is more critical for functional applications. In this context, antioxidant activity serves as a key indicator of bioactive compound preservation.

The highest antioxidant activity was observed under the same optimal condition (35°C, 20 minutes), with an $IC_{50}$ value of approximately 45 ppm, indicating very strong antioxidant capacity .

The strong antioxidant activity is attributed to the presence of:

- Phenolic compounds
- Flavonoids
- Chalcones

These compounds are highly sensitive to processing conditions, and their preservation depends on maintaining a balance between extraction efficiency and degradation risk.

### 2.3.3 Process Efficiency and Industrial Implications

From a process engineering perspective, the findings of this study highlight several important implications:

- Moderate conditions are optimal: High temperatures and long extraction times are not necessary, which reduces energy consumption.
- Rapid extraction kinetics: UAE enables efficient extraction within a short time frame (20 minutes), improving throughput.
- High-quality extract preservation: Optimized conditions ensure that bioactive compounds remain intact, supporting functional applications.
- Scalability potential: The simplicity and efficiency of UAE make it suitable for industrial-scale operations, particularly when integrated with downstream processes such as concentration and formulation.

### 2.4 Summary of Extraction Performance

Overall, UAE demonstrates significant advantages as an extraction method for ashitaba leaves. The combination of moderate temperature, short extraction time, and appropriate solvent selection results in:

- High extraction yield
- Strong antioxidant activity
- Efficient and sustainable processing

These findings provide a solid foundation for subsequent formulation processes, including encapsulation and effervescent product development, where extract quality plays a critical role in determining final product performance.

## 3. CONCENTRATION AND DRYING OF EXTRACT

### 3.1 Solvent Evaporation and Extract Concentration

Following the extraction stage, the resulting liquid extract contains a significant amount of solvent that must be removed to obtain a concentrated product suitable for further processing. Solvent evaporation is therefore a critical step that directly influences extract stability, handling, and downstream formulation.

In this study, solvent removal was carried out using a rotary evaporator under controlled conditions (approximately 50°C and reduced pressure). The use of reduced pressure allows solvent evaporation at lower temperatures, thereby minimizing thermal degradation of bioactive compounds. This is particularly important for Ashitaba (Angelica keiskei) extract, which contains thermolabile constituents such as flavonoids and chalcones .

The principle of rotary evaporation involves the continuous rotation of the flask, which increases the surface area of the liquid and enhances heat transfer. Simultaneously, vacuum conditions reduce the boiling point of the solvent, enabling efficient removal without exposing the extract to excessive heat. Compared to open evaporation methods, this technique offers:

- Faster solvent removal
- Reduced oxidation risk
- Better preservation of bioactive compounds

These advantages have been widely reported in the processing of plant extracts, where maintaining functional integrity is essential for nutraceutical applications (Chemat et al., 2017).

### 3.2 Vacuum Drying Technology

After concentration, further moisture removal is often required to improve the stability and shelf life of the extract.

In this context, vacuum drying is employed as an effective technique to convert concentrated extracts into semi-solid or dry forms suitable for formulation into capsules or effervescent products.

Vacuum drying operates under reduced pressure, which lowers the boiling point of water and allows drying to occur at relatively low temperatures. This condition is particularly beneficial for preserving heat-sensitive bioactive compounds. Compared to conventional drying methods, vacuum drying offers several advantages:

- Reduced thermal degradation
- Lower oxidation rate
- Improved retention of volatile and sensitive compounds

The application of vacuum drying in plant extract processing has been shown to maintain higher levels of phenolic and flavonoid compounds compared to high-temperature drying methods (Zhang et al., 2019). This is especially relevant for ashitaba extract, where the functional properties are closely linked to the stability of these compounds.

In small-scale agroindustrial systems, vacuum drying is also advantageous due to its relatively simple operation and scalability. The use of multi-rack vacuum dryers enables batch processing with controlled temperature and pressure conditions, making it suitable for pilot-scale and small-scale production.

### 3.3 Stability of Bioactive Compounds During Processing

One of the main challenges in post-extraction processing is maintaining the stability of bioactive compounds. Phenolic compounds, flavonoids, and chalcones are known to be sensitive to:

- Heat
- Oxygen exposure
- Light
- Moisture

During evaporation and drying, these factors can lead to structural degradation, oxidation, or loss of functional activity (Dai & Mumper, 2010).

In the case of ashitaba extract, the use of controlled evaporation (low temperature and vacuum conditions) helps to preserve antioxidant activity by minimizing exposure to high thermal energy. Similarly, vacuum drying reduces the presence of oxygen and limits oxidative reactions, thereby maintaining the integrity of bioactive compounds.

Experimental observations indicate that extracts processed under optimized conditions retain strong antioxidant activity, although some reduction may occur compared to fresh extracts. This reduction is generally attributed to:

- Partial degradation of phenolic compounds
- Interaction with residual moisture
- Structural changes during drying

Nevertheless, the retained antioxidant activity remains within a functional range, allowing the extract to be effectively used in nutraceutical formulations such as effervescent products.

### 3.4 Process Optimization and Industrial Considerations

From an industrial perspective, the integration of evaporation and drying processes must be carefully optimized to balance efficiency and product quality.

Key considerations include:

- Temperature Control: Maintaining moderate temperatures is essential to prevent degradation of thermolabile compounds while ensuring efficient moisture removal.
- Pressure Regulation: Vacuum conditions should be optimized to achieve rapid evaporation without causing excessive foaming or loss of volatile components.
- Energy Efficiency: The combination of rotary evaporation and vacuum drying offers a relatively energy-efficient solution compared to conventional drying methods, particularly when operated under optimized conditions.
- Product Consistency: Uniform drying is necessary to ensure consistent moisture content, which is critical for downstream processing, especially in effervescent formulations that are highly sensitive to moisture.

### 3.5 Role in Downstream Formulation

The quality of the concentrated and dried extract plays a crucial role in determining the success of subsequent formulation processes. In particular:

- Moisture content affects flowability and stability
- Particle characteristics influence mixing and granulation
- Bioactive retention determines functional efficacy

For effervescent systems, low moisture content is especially critical, as the presence of water can trigger premature reactions between acid and base components. Therefore, proper drying not only improves shelf life but also ensures the stability of the final product.

### 3.6 Summary

The combination of rotary evaporation and vacuum drying provides an effective approach for processing ashitaba extract into a stable and functional intermediate product. These techniques enable:

- Efficient solvent removal
- Preservation of bioactive compounds
- Improved stability for further formulation

By maintaining controlled processing conditions, it is possible to retain the functional properties of ashitaba while preparing the extract for incorporation into advanced delivery systems such as capsules and effervescent formulations.

## 4. FORMULATION INTO CAPSULE DOSAGE FORM

### 4.1 Formulation Design of Ashitaba Extract Capsules

The transformation of plant extracts into solid dosage forms is a crucial step in enhancing their stability, dosage accuracy, and consumer acceptability. Among various delivery systems, capsule dosage forms are widely used for herbal supplements due to their simplicity, flexibility, and compatibility with a wide range of bioactive compounds.

In this study, the concentrated and dried extract of Ashitaba (Angelica keiskei) obtained from optimized extraction and drying processes was formulated into capsule dosage form. The formulation design aimed to ensure:

- Uniform distribution of active compounds
- Adequate flowability for encapsulation
- Stability during storage
- Ease of consumption

The development process began with the characterization of the dried extract, including moisture content, particle size, and flow properties. These parameters are critical in determining the suitability of the extract for encapsulation. Plant extracts typically exhibit poor flowability and high hygroscopicity, which necessitate the use of appropriate excipients to improve processing performance (Aulton & Taylor, 2018).

The formulation strategy involved blending the ashitaba extract with selected excipients to produce a homogeneous powder mixture suitable for encapsulation. The final blend was then filled into hard gelatin or hydroxypropyl methylcellulose (HPMC) capsules using manual or semi-automatic capsule filling systems.

## 4.2 Role of Excipients in Capsule Formulation

Excipients play a fundamental role in ensuring the quality and performance of capsule formulations. In plant-based supplements, excipients are not only used to facilitate processing but also to enhance stability and bioavailability.

### 4.2.1 Fillers and Diluents

Fillers such as maltodextrin are commonly used to increase the bulk volume of the formulation and improve flow properties. Maltodextrin is particularly suitable for plant extract formulations due to its:

- Good solubility
- Low hygroscopicity compared to crude extracts
- Compatibility with bioactive compounds

The addition of fillers helps to standardize capsule weight and ensure uniform dosing, which is essential for maintaining product consistency.

### 4.2.2 Binders and Flow Enhancers

Binders such as polyvinylpyrrolidone (PVP) may be incorporated to improve particle cohesion and prevent segregation during mixing. In addition, flow enhancers or glidants (e.g., colloidal silica) can be used to reduce interparticle friction and improve powder flowability.

Improved flowability is critical for achieving consistent capsule filling and preventing weight variation. Poor flow properties can lead to operational inefficiencies and variability in active compound distribution (Rowe et al., 2009).

### 4.2.3 Lubricants

Lubricants such as polyethylene glycol (PEG) or magnesium stearate are used to reduce friction between the powder and equipment surfaces during encapsulation. This facilitates smooth filling and prevents sticking or clogging in capsule-filling machines.

However, the concentration of lubricants must be carefully controlled, as excessive use may negatively affect dissolution and bioavailability of the active compounds.

### 4.2.4 Capsule Shell Materials

Capsule shells can be made from:

- Gelatin (animal-derived)
- Hydroxypropyl methylcellulose (HPMC) (plant-based)

HPMC capsules are increasingly preferred for plant-based supplements due to their:

- Vegetarian compatibility
- Better moisture resistance
- Improved stability under varying environmental conditions

The choice of capsule shell can influence product stability, especially for hygroscopic formulations such as plant extracts.

## 4.3 Homogeneity and Quality Control

One of the most critical aspects of capsule formulation is achieving content uniformity and homogeneity.

This ensures that each capsule contains a consistent amount of active compounds, which is essential for both efficacy and regulatory compliance.

Homogeneity is influenced by several factors:

- Particle size distribution
- Mixing method and duration
- Density differences between components

To achieve optimal homogeneity, the blending process must be carefully controlled. Techniques such as geometric dilution are often used to ensure even distribution of active ingredients, particularly when the extract constitutes a small proportion of the total formulation.

Quality control tests for capsule formulations typically include:

- Weight uniformity
- Content uniformity
- Moisture content
- Disintegration time

These parameters are essential for ensuring product consistency and performance. Studies have shown that proper formulation design and mixing strategies can significantly improve uniformity and reduce variability in herbal capsule products (Aulton & Taylor, 2018).

### 4.4 Stability Considerations

The stability of capsule formulations is influenced by both the properties of the extract and the formulation components. Ashitaba extract contains phenolic compounds and flavonoids that are sensitive to:

- Moisture
- Oxygen
- Temperature

The use of appropriate excipients and packaging materials is therefore essential to maintain product stability. Low-moisture formulations and the use of moisture-resistant capsule shells can help prevent degradation and extend shelf life. In addition, storage conditions such as controlled temperature and humidity are critical for preserving the functional properties of the product.

Properly formulated capsules can maintain bioactive stability over extended periods, making them suitable for commercial distribution.

### 4.5 Advantages of Capsule Dosage Form

Capsules offer several advantages for delivering plant-based extracts, particularly in comparison to traditional herbal preparations:

- Accurate Dosage: Capsules provide precise dosing, ensuring consistent intake of bioactive compounds.
- Improved Stability: Encapsulation protects sensitive compounds from environmental factors such as light and oxygen.
- Enhanced Consumer Acceptability: Capsules are easy to swallow and eliminate the need for preparation, unlike decoctions or infusions.
- Flexibility in Formulation: Capsules can accommodate a wide range of formulations, including powders, granules, and semi-solid extracts.
- Compatibility with Industrial Production: Capsule filling is a well-established process that can be easily scaled up for mass production.

### 4.6 Integration with Downstream Product Development

Although capsule formulation provides a stable and convenient dosage form, it represents only one pathway for delivering ashitaba bioactive compounds. In this study, capsule formulation serves as an intermediate step toward more advanced delivery systems, such as effervescent formulations.

The knowledge gained from capsule formulation particularly regarding excipient selection, flowability, and stability provides a foundation for optimizing more complex systems. This integration highlights the importance of a holistic approach in developing functional supplements, where each processing stage contributes to the overall product quality.

### 4.7 Summary

The formulation of ashitaba extract into capsule dosage form demonstrates the feasibility of transforming plant-based extracts into stable, standardized, and consumer-friendly products. Through careful selection of excipients and optimization of mixing processes, it is possible to achieve:

- Good flowability and processability

- Uniform distribution of active compounds
- Enhanced stability and shelf life

Capsule dosage forms thus represent an essential component in the development of functional plant-based supplements and provide a foundation for further innovation in delivery systems.

## 5. DEVELOPMENT OF EFFERVESCENT FORMULATION

### 5.1 Principle of Effervescent Systems

Effervescent formulations are widely used in pharmaceutical and nutraceutical applications as an advanced delivery system designed to improve solubility, dissolution rate, and consumer acceptability of active compounds. The fundamental principle of effervescent systems lies in an acid–base reaction that occurs upon contact with water, resulting in the rapid release of carbon dioxide ($CO_2$) gas.

This reaction typically involves organic acids, such as citric acid or tartaric acid, and a carbonate or bicarbonate base, most commonly sodium bicarbonate. When dissolved in water, these components react to form $CO_2$, which enhances the dispersion and dissolution of active compounds, leading to improved bioavailability (Rowe et al., 2009).

For plant-based extracts such as Ashitaba (Angelica keiskei), effervescent systems offer additional advantages, including:

- Masking of bitter taste
- Faster release of bioactive compounds
- Improved patient compliance

These characteristics make effervescent formulations particularly suitable for functional supplements derived from herbal extracts.

### 5.2 Formulation Components and Their Functional Roles

The development of ashitaba effervescent granules in this study involved a multi-component system consisting of active extract, acid-base reactants, and supporting excipients.

### 5.2.1 Acid Components: Citric Acid and Tartaric Acid

Organic acids serve as proton donors in the effervescent reaction. In this formulation, citric acid and tartaric acid were used in combination to achieve optimal performance.

Citric acid contributes to:

- Rapid dissolution
- Pleasant sour taste
- Enhanced solubility of active compounds

Tartaric acid, on the other hand, plays a role in:

- Reducing stickiness during granulation
- Improving powder stability
- Balancing the effervescence reaction

The use of a dual-acid system is widely recommended because it minimizes formulation problems associated with single-acid systems, such as excessive hygroscopicity or poor mechanical properties (Rowe et al., 2009).

### 5.2.2 Base Component: Sodium Bicarbonate

Sodium bicarbonate ($NaHCO_3$) is the primary base used in effervescent formulations. It reacts with organic acids to produce carbon dioxide, water, and corresponding salts. The efficiency of this reaction directly affects the dissolution rate and sensory characteristics of the final product.

In addition to its role in $CO_2$ generation, sodium bicarbonate contributes to:

- pH adjustment
- Improved mouthfeel
- Enhanced dispersion of active compounds

The ratio between acid and base components must be carefully controlled to ensure complete reaction without leaving residual acidity or alkalinity.

### 5.2.3 Supporting Excipients

The formulation also incorporated several excipients to improve physical and functional properties:

- Maltodextrin: filler and carrier, improves flowability and reduces hygroscopicity
- Polyvinylpyrrolidone (PVP): binder, enhances granule cohesion
- Aspartame: sweetener, masks bitterness of extract
- Polyethylene glycol (PEG 6000): lubricant, facilitates processing

These excipients play a crucial role in ensuring that the formulation is not only functional but also manufacturable and acceptable to consumers.

### 5.3 Optimization of Formulation

Six formulations (F1–F6) were developed with varying ratios of extract and effervescent components to determine the optimal composition (Table 1).

**Table 1.** Formulation of Ashitaba Effervescent Granules

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Ashitaba extract | 60 | 120 | 180 | 240 | 300 | 360 |
| Citric acid | 340 | 320 | 300 | 280 | 260 | 240 |
| Tartaric acid | 460 | 440 | 420 | 400 | 380 | 360 |
| Sodium bicarbonate | 620 | 600 | 580 | 560 | 540 | 520 |
| PVP | 50 | 50 | 50 | 50 | 50 | 50 |
| Aspartame | 20 | 20 | 20 | 20 | 20 | 20 |
| Maltodextrin | 410 | 410 | 410 | 410 | 410 | 410 |
| PEG 6000 | 40 | 40 | 40 | 40 | 40 | 40 |
| **Total (mg)** | **2000** | **2000** | **2000** | **2000** | **2000** | **2000** |

#### 5.3.1 Moisture Content

Moisture content ranged from approximately 4.67% to 8.48%, with only certain formulations meeting the desired standard (<5%) .

Higher moisture content was associated with increased extract concentration, due to:

- Hygroscopic nature of plant extract
- Residual water from processing

Moisture control is critical in effervescent systems, as excess water can trigger premature acid–base reactions and compromise product stability.

### 5.3.2 Flowability and Compressibility

Flow properties are essential for efficient processing and uniform dosing. Among the tested formulations, F3 exhibited the best flowability, with:

- Flow time ≈ 11.78 seconds
- Compressibility ≈ 10%

These values indicate good handling characteristics and suitability for industrial-scale production .

### 5.3.3 pH and Organoleptic Properties

The pH of the effervescent solutions ranged from 4.2 to 4.6, indicating a slightly acidic environment. This pH range is favorable for:

- Stability of phenolic compounds
- Acceptable taste profile

The combination of acids and sweeteners contributed to improved sensory acceptability, effectively masking the inherent bitterness of ashitaba extract.

## 5.4 Dissolution Time and Functional Performance

Dissolution time is a key parameter in evaluating effervescent formulations, as it reflects the efficiency of the acid–base reaction and the release of active compounds.

The tested formulations demonstrated rapid dissolution upon contact with water, which can be attributed to:

- Efficient $CO_2$ generation
- Proper acid–base ratio
- Adequate granule porosity

Rapid dissolution enhances the availability of bioactive compounds and improves user convenience. According to pharmaceutics standards, effervescent products are expected to dissolve within a few minutes, and the formulations developed in this study meet this requirement.

### 5.5 Stability of Effervescent Formulation

Stability is one of the most critical challenges in effervescent product development. These systems are highly sensitive to environmental conditions, particularly:

- Humidity
- Temperature
- Packaging integrity

The presence of moisture can initiate premature reactions between acid and base components, leading to:

- Loss of effervescence
- Reduced product efficacy
- Physical degradation

In this study, stability considerations were addressed through:

- Optimization of moisture content
- Use of appropriate excipients
- Controlled processing conditions

Despite some reduction in antioxidant activity compared to the crude extract, the effervescent product retained functional properties, demonstrating its potential as a nutraceutical product .

### 5.6 Optimal Formulation and Trade-Off Analysis

The best formulation identified was F3, which provided the most balanced performance in terms of:

- Flowability
- Moisture content
- Dissolution behavior
- Antioxidant activity

This result highlights the importance of balancing functional and physical properties in formulation design.

A key trade-off was observed:

- Higher extract concentration → increased bioactivity but reduced stability

- Lower extract concentration → improved stability but lower functionality

The selected formulation represents an optimal compromise between these competing factors, which is a common challenge in the development of plant-based functional products.

## 5.7 Industrial Perspective and Applicability

From an industrial standpoint, the developed effervescent formulation demonstrates strong potential for commercialization.

Key advantages include:

- Rapid and convenient consumption
- Improved sensory properties
- Scalable production process

However, several challenges must be addressed for large-scale production:

- Strict humidity control during manufacturing
- Use of moisture-resistant packaging (e.g., aluminum foil, desiccants)
- Consistent raw material quality

The integration of optimized extraction, drying, and formulation processes provides a robust framework for developing high-value functional supplements from ashitaba.

## 5.8 Summary

The development of effervescent formulations from ashitaba extract demonstrates a successful transformation of plant-based bioactive compounds into a stable, functional, and consumer-friendly product. Through careful selection of components and optimization of formulation parameters, it is possible to achieve:

- Rapid dissolution
- Acceptable sensory quality
- Retention of functional properties

This approach highlights the potential of effervescent systems as an innovative delivery platform for plant-based nutraceuticals.

## 6. INDUSTRIAL AND SCALE-UP CONSIDERATIONS

### 6.1 Small-Scale Plant Design for Ashitaba Processing

The industrial application of Ashitaba (Angelica keiskei) extract requires an integrated processing system that connects upstream extraction with downstream formulation into functional products such as capsules and effervescent granules. In the context of small-to-medium enterprises (SMEs), a small-scale processing plant design offers a feasible and economically viable approach for commercialization.

Based on the developed process, the production system can be divided into several key stages:

- Raw material preparation (drying and milling of ashitaba leaves and stems)
- Extraction using Ultrasonic-Assisted Extraction (UAE)
- Filtration and solvent recovery
- Concentration using rotary evaporation
- Drying using vacuum drying
- Formulation into capsule and effervescent products

The selection of equipment is critical to ensure process efficiency while maintaining product quality. For instance, the use of a multi-rack vacuum dryer with moderate capacity (e.g., 10 racks) enables batch drying under controlled temperature and pressure conditions. This type of equipment is suitable for small-scale operations due to its relatively low capital cost and operational flexibility.

Similarly, UAE systems can be implemented using ultrasonic bath or probe-type devices, which are commercially available and adaptable to different production scales. Compared to conventional extraction systems, UAE equipment requires lower energy input and shorter processing time, contributing to overall process efficiency (Chemat et al., 2017).

The integration of these unit operations into a semi-continuous production line allows for improved workflow and reduced processing time, which is essential for maintaining product consistency in small-scale industrial settings.

## 6.2 Cost Efficiency and Economic Considerations

Cost efficiency is a major factor in determining the feasibility of scaling up plant-based supplement production. The economic performance of the process is influenced by both capital expenditure (CAPEX) and operational expenditure (OPEX).

### 6.2.1 Capital Investment

The initial investment for a small-scale ashitaba processing plant includes:

- Ultrasonic extraction equipment
- Rotary evaporator
- Vacuum dryer
- Mixing and granulation equipment
- Capsule filling machine

Among these, the vacuum dryer represents one of the most significant investments. However, its multifunctional capability (drying both raw materials and extracts) reduces the need for additional equipment, thereby optimizing capital costs.

### 6.2.2 Operational Costs

Operational costs are primarily associated with:

- Energy consumption
- Solvent usage (ethanol)
- Labor
- Raw materials

The use of UAE significantly reduces extraction time and energy consumption compared to conventional methods, leading to lower operational costs. Additionally, ethanol can be recovered and reused through evaporation systems, further improving cost efficiency.

From a process optimization perspective, operating at moderate temperatures (e.g., 35°C during extraction) and short processing times minimizes energy requirements while maintaining high product quality.

This balance between efficiency and quality is essential for achieving economic sustainability.

### 6.2.3 Value Addition and Product Diversification

One of the key advantages of this system is the ability to produce multiple product forms (capsules and effervescent formulations) from a single raw material. This diversification:

- Increases market reach
- Enhances product value
- Reduces economic risk

Effervescent products, in particular, have higher added value due to their convenience and functional appeal, making them attractive for premium markets.

## 6.3 Challenges in Mass Production

Despite the promising potential, scaling up the production of ashitaba-based supplements presents several technical and operational challenges.

### 6.3.1 Raw Material Variability

One of the primary challenges is the variability in raw material quality, which can be influenced by:

- Growing conditions
- Harvesting time
- Post-harvest handling

Variations in bioactive compound content can affect extraction efficiency and final product quality. Standardization of raw materials is therefore essential to ensure consistent performance (Putnik et al., 2018).

### 6.3.2 Process Control and Optimization

Scaling up UAE processes requires careful control of:

- Ultrasonic power distribution
- Temperature uniformity
- Solvent-to-solid ratio

In larger systems, uneven energy distribution may reduce extraction efficiency. Therefore, process parameters must be re-optimized during scale-up to maintain performance.

Similarly, drying processes must ensure uniform moisture removal to prevent product instability, particularly for effervescent formulations that are highly sensitive to moisture.

### 6.3.3 Moisture Sensitivity in Effervescent Products

Effervescent formulations present unique challenges due to their hygroscopic nature. Exposure to humidity can trigger premature acid–base reactions, leading to:

- Loss of effervescence
- Reduced product shelf life

To address this issue, strict environmental control is required during production, including:

- Low-humidity processing environments
- Use of dehumidifiers
- Moisture-resistant packaging (e.g., aluminum foil, desiccants)

### 6.3.4 Scale-Up of Mixing and Granulation

Achieving uniform mixing at larger scales is more complex due to:

- Increased batch size
- Differences in particle properties

Inadequate mixing can lead to segregation and variability in product composition. Advanced mixing technologies and process control strategies are required to ensure homogeneity in large-scale production.

## 6.4 Industrial Feasibility and Future Outlook

Despite these challenges, the integration of optimized extraction, drying, and formulation processes provides a strong foundation for industrial application. The use of efficient technologies such as UAE and vacuum drying supports the development of a sustainable and scalable production system.

Future improvements may include:

- Continuous extraction systems

- Advanced drying technologies (e.g., spray drying, freeze drying)
- Automation of formulation processes

In addition, the growing demand for plant-based functional supplements presents significant market opportunities, particularly in health-conscious consumer segments.

## CONCLUSION

The industrialization of ashitaba-based functional supplements is feasible through the implementation of a well-designed small-scale processing system. By optimizing equipment selection, process parameters, and formulation strategies, it is possible to achieve:

- Cost-efficient production
- High product quality
- Scalable operations

However, successful scale-up requires careful attention to raw material consistency, process control, and environmental conditions, particularly for moisture-sensitive products such as effervescent formulations.

## REFERENCES

Aulton, M. E., & Taylor, K. (2018). Aulton's pharmaceutics: The design and manufacture of medicines (5th ed.). Elsevier.

Baba, K., Nakata, K., Taniguchi, M., Kido, T., & Kozawa, M. (2007). Chalcones from Angelica keiskei. Phytochemistry, 30(3), 973–980. https://doi.org/10.1016/0031-9422(91)85254-T

Chemat, F., Rombaut, N., Sicaire, A. G., Meullemiestre, A., Fabiano-Tixier, A. S., & Abert-Vian, M. (2017). Ultrasound assisted extraction of food and natural products. Ultrasonics Sonochemistry, 34, 540–560. https://doi.org/10.1016/j.ultsonch.2016.06.035

Dai, J., & Mumper, R. J. (2010). Plant phenolics: Extraction, analysis and their antioxidant and anticancer properties. Molecules, 15(10), 7313–7352. https://doi.org/10.3390/molecules15107313

Granato, D., Barba, F. J., Kovačević, D. B., Lorenzo, J. M., Cruz, A. G., & Putnik, P. (2020). Functional foods: Product development, technological trends, efficacy testing, and safety. Annual Review of Food Science and Technology, 11, 93–118. https://doi.org/10.1146/annurev-food-032519-051708

Putnik, P., Lorenzo, J. M., Barba, F. J., Roohinejad, S., Režek Jambrak, A., Granato, D., & Bursać Kovačević, D. (2018). Novel food processing and extraction technologies of high-added value compounds. Trends in Food Science & Technology, 75, 63–75.

Rowe, R. C., Sheskey, P. J., & Quinn, M. E. (2009). Handbook of pharmaceutical excipients (6th ed.). Pharmaceutical Press.

Saha, S., Roy, S., & Roy, S. (2020). Nutraceuticals: An emerging therapeutic approach against chronic diseases. Current Pharmaceutical Biotechnology, 21(15), 1496–1508.

Shahidi, F. (2012). Nutraceuticals, functional foods and dietary supplements in health and disease. Journal of Food Drug Analysis, 20(1), 226–230.

Vilkhu, K., Mawson, R., Simons, L., & Bates, D. (2008). Applications and opportunities for ultrasound assisted extraction in the food industry. Innovative Food Science & Emerging Technologies, 9(2), 161–169. https://doi.org/10.1016/j.ifset.2007.04.014

Zhang, Y., Li, S., Wang, X., Zhang, L., & Cheung, P. C. K. (2019). Advances in Angelica keiskei bioactive compounds and their pharmacological activities. Food Chemistry, 284, 152–161.

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