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PENTACYCLIC TRITERPENOIDS:

EXPLORING THE DIVERSE PHARMACOLOGICAL POTENTIAL

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Abstract: Triterpenoids are a class of natural compounds with a wide range of chemical structures and biological activities. Pentacyclic triterpenoids, a distinct subclass with a distinct five-ring structure, are a promising therapeutic target. Betulinic acid, oleanolic acid, and ursolic acid, for example, have shown promising therapeutic potential in a variety of organisms. Betulinic acid has cytotoxic effects on cancer cells, making it a potential chemotherapy agent. Ursolic acid has antioxidant, anti-inflammatory, anti-diabetic, and anticancer properties, whereas oleanolic acid has anti-inflammatory, hepatoprotective, and anticancer properties. These compounds also play important ecological roles in plant defence mechanisms and have allelopathic properties, influencing the growth and behaviour of neighbouring plants. Their diverse pharmacological properties make them appealing drug discovery leads, with researchers investigating structure-activity relationships and optimising biological activities.

Index Terms **- Pentacyclic triterpenoid, Anti-inflammatory, Anticancer, Antimicrobial, Antioxidant, Immunomodulatory**

I. INTRODUCTION

Triterpenoids are an intriguing group of natural compounds that have captured the attention of scientists due to their diverse chemical structures and wide range of biological activities. These compounds are derived from isoprene units[1] and can be found abundantly in nature, spanning across various kingdoms of life, including plants, fungi, and even certain animals[2]. Their prevalence in such diverse organisms highlights their significance and widespread occurrence in the natural world. From lush rainforests to the depths of marine ecosystems, triterpenoids can be discovered in a remarkable array of plant species, as well as in fungi and other organisms that have evolved to harness their potent properties[3].

Pentacyclic triterpenoids, a distinct subclass of triterpenoids, are characterized by their unique five-ring structure. This structural feature sets them apart from other triterpenoids and contributes to their diverse chemical properties and biological activities. Within the class of pentacyclic triterpenoids, there are numerous well-known and extensively studied compounds that have showcased their potential in various fields.

One such compound is betulinic acid, which is derived from betulin, a triterpenoid found in the bark of white birch trees. Betulinic acid has attracted attention for its potential anticancer properties, as it has shown cytotoxic effects against different cancer cell lines and has emerged as a promising candidate for chemotherapy[4].

Another notable pentacyclic triterpenoid is oleanolic acid, which is widely distributed in various plant species, including olive trees, garlic, and medicinal herbs. This compound has been the subject of extensive research due to its anti-inflammatory[5], hepatoprotective[6], and anticancer activities[7]. Studies have indicated its potential in modulating immune responses and inhibiting tumor growth.

Ursolic acid, another well-studied pentacyclic triterpenoid, can be found in numerous plant sources such as apple peels, rosemary, and holy basil. This compound has gained recognition for its diverse pharmacological properties, including antioxidant[8], anti-inflammatory[9], anti-diabetic[10], and anticancer effects[11]. Ursolic acid has demonstrated promise in preclinical studies, exhibiting the ability to inhibit tumor growth and induce apoptosis in cancer cells[12].

Pentacyclic triterpenoids not only exhibit remarkable abundance and diversity in various plant families and natural habitats but also play vital ecological roles[13]. These compounds can be found in a wide range of plant species, from flowering plants to ferns and even mosses. Their presence in significant quantities within plant families such as Asteraceae[14], Rosaceae[15], Lamiaceae[16], and Fabaceae[17] underscores their widespread distribution and biosynthetic capabilities.

The diversity of pentacyclic triterpenoids is equally impressive. Each plant species often produces a unique profile of these compounds, varying in terms of specific structures, substitution patterns, and functional groups present. This chemical diversity contributes to the wide array of biological activities exhibited by pentacyclic triterpenoids.

One of the fascinating aspects of these compounds is their ecological role in plant defense mechanisms. Pentacyclic triterpenoids are known to play a pivotal role in deterring herbivores and protecting plants against pathogenic microorganisms. They can act as potent repellents, feeding deterrents, or even toxins to herbivorous insects and mammals. Furthermore, they can inhibit the growth and development of microbial pathogens, enhancing the plant's resistance to infections[18].

Additionally, some pentacyclic triterpenoids exhibit allelopathic properties, influencing the growth and behavior of neighboring plants. Through these allelochemical interactions, plants can compete for resources and establish their dominance in a given habitat[19].

Apart from their ecological importance, pentacyclic triterpenoids have a long history of use in traditional medicine systems. They have been valued for their medicinal properties and therapeutic benefits for centuries. Traditional uses include their anti-inflammatory effects, which help alleviate pain and reduce swelling, making them valuable in managing conditions such as arthritis and rheumatism[20]. These compounds have also been utilized for their hepatoprotective properties, aiding in the protection and regeneration of liver cells[6]. Additionally, their antimicrobial and antifungal activities have been harnessed to combat various infections and promote healing[21].

Furthermore, the antiviral activity of pentacyclic triterpenoids has attracted attention, particularly in the context of viral infections such as HIV[22] and hepatitis[6]. These compounds have shown inhibitory effects on viral replication, suggesting their potential as antiviral agents.

The diverse pharmacological activities exhibited by pentacyclic triterpenoids make them attractive lead compounds for drug discovery. Researchers are delving into the structure-activity relationships of these compounds, aiming to optimize their biological activities and minimize potential side effects. Moreover, their natural abundance and sustainable sourcing from plant-based materials make them appealing alternatives to synthetic compounds, aligning with the growing interest in green chemistry and environmentally friendly approaches to pharmaceutical research.

II. BIOSYNTHESIS OF PENTACYCLIC TRITERPENOIDS

2.1. Overview of triterpenoid biosynthesis pathway:

Pentacyclic triterpenoids, complex natural compounds with diverse biological activities, are synthesized through intricate pathways in living organisms. Two main biosynthetic pathways, the mevalonic acid (MVA) pathway[23] and the methylerythritol phosphate (MEP) pathway[24], are responsible for the production of these compounds[25].

The MVA pathway, which occurs in the cytosol, begins with the conversion of acetyl-CoA to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), catalyzed by the enzyme HMG-CoA reductase[26]. HMG-CoA is further reduced to mevalonic acid, which undergoes a series of enzymatic reactions to produce isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), the building blocks of triterpenoids. Enzymes such as mevalonate kinase, phosphomevalonate kinase, and mevalonate diphosphate decarboxylase are involved in these reactions[23], [27].

On the other hand, the MEP pathway takes place in plastids and starts with the condensation of pyruvate and glyceraldehyde 3-phosphate, catalyzed by 1-deoxy-D-xylulose 5-phosphate synthase (DXS). This leads to the formation of 1-deoxy-D-xylulose 5-phosphate (DXP), which undergoes further enzymatic reactions to generate isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP)[24], [28].

Once IPP and DMAPP are synthesized through the MVA and MEP pathways, they serve as precursors for the biosynthesis of pentacyclic triterpenoids. The conversion of IPP and DMAPP into pentacyclic triterpenoids involves a series of enzymatic steps, including cyclization, oxidation, and modification reactions[28].

Cyclization reactions are guided by cyclases, which facilitate the folding and formation of the characteristic five-ring structure of pentacyclic triterpenoids. Different cyclases, such as oxidosqualene cyclase, lupeol synthase, and β-amyrin synthase, produce various pentacyclic triterpenoid compounds with distinct structures and properties[29].

After cyclization, oxidation reactions occur, mediated by enzymes like cytochrome P450 monooxygenases. These enzymes introduce functional groups, such as hydroxyl and carboxyl groups, into the pentacyclic triterpenoid backbone, contributing to their diverse biological activities and pharmacological properties[30].

Modification reactions, such as glycosylation, methylation, and acylation, further enhance the structural diversity and bioactivity of pentacyclic triterpenoids. Enzymes like glycosyltransferases, methyltransferases, and acyltransferases are involved in these modifications.

III. CLASSIFICATION AND SOURCES OF PENTACYCLIC TRITERPENOIDS

3.1. Classification based on carbon skeleton and functional groups[31],[32]:

Pentacyclic triterpenoid can be classified based on both their carbon skeleton variations and the functional groups present in their chemical structure. This classification provides valuable insights into their chemical and biological properties.

One common classification of pentacyclic triterpenoid is based on their carbon skeleton variations. Three main carbon skeletons are often recognized: lupane, ursane, and oleanane. These classifications are named after specific triterpenoids that exemplify each skeleton. Lupane-type triterpenoid have a characteristic structure derived from the triterpene lupane, while ursane-type triterpenoid are based on the triterpene ursane, and oleanane-type triterpenoids derive from the triterpene oleanane.

Lupane-type triterpenoids are characterized by their lupane skeleton, which consists of a pentacyclic structure with a single six-membered ring and four five-membered rings. This carbon skeleton variation gives rise to various lupane-type triterpenoids found in natural sources. These compounds often exhibit diverse biological activities, including anti-inflammatory, antiviral, and antitumor properties. Examples of lupane-type triterpenoids include betulinic acid and lupeol[33].

Ursane-type triterpenoids derive their name from the ursane skeleton, which features a pentacyclic structure with a single six-membered ring and four five-membered rings, similar to the lupane skeleton. However, the specific arrangement of the rings differs, leading to distinct chemical and biological properties. Ursane-type triterpenoids are known for their anti-inflammatory, anticancer, and hepatoprotective activities. Ursolic acid and oleanolic acid are well-known examples of ursane-type triterpenoids[34].
Oleanane-type triterpenoids are characterized by the oleanane skeleton, which also consists of a pentacyclic structure but with a different arrangement of the rings compared to lupane and ursane. Oleanane-type triterpenoids are widely distributed in nature and have been extensively studied for their medicinal properties. These compounds exhibit a broad range of activities, including anti-inflammatory, antidiabetic, and antimicrobial effects. Examples of oleanane-type triterpenoids include glycyrrhizin and maslinic acid[35].

3.2. Representative examples and natural sources:
Pentacyclic triterpenoids, with their diverse chemical structures and biological activities, are found abundantly in various natural sources. These compounds have been identified in plants, fungi, and even marine organisms, highlighting their wide distribution across different kingdoms of life.
In the plant kingdom, numerous species have been recognized as rich sources of pentacyclic triterpenoid. For instance, plants belonging to the family Asteraceae, such as *Calendula officinalis* (marigold), have been found to contain significant amounts of pentacyclic triterpenoids. These include compounds like oleanolic acid and ursolic acid, which are renowned for their medicinal properties[36].
Other plant families that are known to produce pentacyclic triterpenoids include Rosaceae (roses)[37], Lamiaceae (mint family)[38], and Fabaceae (legume family)[39]. In Rosaceae, the fruit peel of apples (*Malus domestica*) is a notable source of triterpenoids, including ursolic acid[32]. The Lamiaceae family includes plants like *Salvia officinalis* (common sage), which contains triterpenoids such as betulinic acid[40]. Fabaceae plants like *Glycyrrhiza glabra* (licorice) are renowned for glycyrrhizin, a pentacyclic triterpenoid with various medicinal properties[41].
Furthermore, certain fungi have also been found to produce pentacyclic triterpenoids. Ganoderma lucidum (reishi mushroom), a well-known medicinal mushroom, contains triterpenoids known as ganoderic acids[42]. These compounds have shown potential in various therapeutic applications, including anticancer and immunomodulatory effects[43].
In addition to plants and fungi, pentacyclic triterpenoids have been discovered in marine organisms as well. Some marine sponges, for instance, have been found to produce triterpenoid compounds with unique structures and biological activities. These marine-derived triterpenoids offer exciting prospects for drug discovery and development[44].
The distribution of pentacyclic triterpenoids in specific plant families and geographical regions is also noteworthy. While these compounds can be found in various plant families, certain families have been identified as particularly rich sources. For example, the Asteraceae family, which includes plants like daisies and sunflowers, has been extensively studied for its triterpenoid content. Similarly, the Fabaceae family, known for its leguminous plants, has been recognized for the presence of specific triterpenoids, such as glycyrrhizin[45].
Geographical factors also play a role in the distribution of pentacyclic triterpenoids. Certain plant species rich in these compounds may be more prevalent in specific regions or ecosystems. For instance, certain species of the genus Boswellia, known for their pentacyclic triterpenoid content[46], are found predominantly in regions like the Arabian Peninsula and India.

IV. BIOLOGICAL ACTIVITIES AND PHARMACOLOGICAL POTENTIAL

4.1. Anti-inflammatory and immunomodulatory effects:
Pentacyclic triterpenoids have garnered significant attention for their potent anti-inflammatory properties and their ability to modulate the immune system[43]. These natural compounds have demonstrated promising effects in alleviating inflammation and regulating immune responses, making them valuable candidates for therapeutic interventions.
One of the key aspects of the anti-inflammatory effects of pentacyclic triterpenoids is their ability to inhibit pro-inflammatory cytokines and enzymes. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), play a crucial role in initiating and amplifying inflammatory responses. Studies have shown that pentacyclic triterpenoids can effectively suppress the production and release of these inflammatory cytokines, thereby attenuating the inflammatory cascade. By inhibiting the activity of these pro-inflammatory mediators, pentacyclic triterpenoids help reduce tissue damage, edema, and pain associated with inflammatory conditions[47].
In addition to their effects on cytokines, pentacyclic triterpenoids also exert immunomodulatory effects by influencing the function of immune cells[48]. These compounds can modulate the activity of various immune cell types, including macrophages, dendritic cells, and lymphocytes. For instance, pentacyclic triterpenoids have been found to inhibit the activation of macrophages, leading to a reduction in the production of inflammatory mediators such as nitric oxide and prostaglandins. This anti-inflammatory effect helps restore the balance in immune responses and prevents excessive immune cell activation, which is often associated with chronic inflammation.

4.2. Anticancer and antitumor properties: Pentacyclic triterpenoids have gained considerable attention for their promising anticancer properties, demonstrating potential as effective agents in the fight against cancer. These natural compounds have shown significant cytotoxicity against cancer cells, the ability to induce apoptosis (programmed cell death), and the capacity to inhibit tumor progression[4],[11].

One of the notable aspects of pentacyclic triterpenoids is their cytotoxicity against cancer cells. Numerous studies have reported their ability to selectively target cancer cells while sparing healthy cells, making them attractive candidates for cancer treatment. These compounds have demonstrated potent cytotoxic effects by inhibiting cell proliferation, inducing cell cycle arrest, and promoting cell death in various cancer cell lines. This cytotoxic activity has been observed in different types of cancer, including breast, lung, colon, prostate, and liver cancer[49], [50].

In addition to their cytotoxic effects, pentacyclic triterpenoids have shown the ability to induce apoptosis in cancer cells. Apoptosis is a natural process that eliminates damaged or abnormal cells from the body. Pentacyclic triterpenoids have been found to trigger apoptotic pathways in cancer cells, leading to their programmed death[51]. These compounds can modulate the expression of key regulatory proteins involved in apoptosis, such as Bcl-2 family proteins and caspases, which play a crucial role in the initiation and execution of apoptosis[52]. By promoting apoptosis, pentacyclic triterpenoids help to eliminate cancer cells and inhibit tumor growth.

Furthermore, pentacyclic triterpenoids exhibit the potential to target specific signaling pathways that are dysregulated in cancer development and metastasis[53]. These compounds can interfere with key signaling pathways involved in cell survival, proliferation, angiogenesis, and metastasis. For example, they have been shown to inhibit the activation of nuclear factor-kappa B (NF-κB), a transcription factor implicated in cancer cell survival and inflammation. By suppressing NF-κB activity, pentacyclic triterpenoids disrupt the pro-survival signals in cancer cells and enhance their sensitivity to apoptotic stimuli[54].

4.3. Antioxidant and hepatoprotective activities[55], [56], [57]:

Pentacyclic triterpenoids possess potent antioxidant properties that protect cells from oxidative stress by scavenging reactive oxygen species (ROS) and inhibiting oxidative damage to biomolecules. They directly neutralize ROS by donating hydrogen atoms or electrons, preventing the propagation of oxidative reactions. Additionally, they enhance the activity of endogenous antioxidant enzymes, reinforcing the cellular defense system against ROS. By chelating metal ions involved in ROS generation, they reduce oxidative stress and cellular damage. These antioxidant properties contribute to the hepatoprotective effects of pentacyclic triterpenoids by preserving cell membrane integrity and enhancing detoxification enzymes, such as glutathione S-transferases. Moreover, they modulate inflammatory pathways, reducing inflammation and safeguarding liver cells from inflammatory damage.

4.4. Antimicrobial and antiviral effects:

Pentacyclic triterpenoids exhibit a wide range of antimicrobial activities against various microorganisms, including bacteria, fungi, and parasites. These compounds have shown promising potential as natural agents for combating infectious diseases.

When it comes to bacteria, pentacyclic triterpenoids have demonstrated significant antibacterial effects against both Gram-positive and Gram-negative bacteria[58]. They act by disrupting bacterial cell membranes, inhibiting essential enzymatic processes, and interfering with bacterial cell wall synthesis[59]. These mechanisms contribute to their bactericidal or bacteriostatic effects, depending on the specific compound and bacterial strain.

In terms of fungi, pentacyclic triterpenoids exhibit potent antifungal activities against a broad spectrum of fungal pathogens. They have been found to inhibit fungal growth, disrupt fungal cell membranes, and interfere with fungal cell wall synthesis. These mechanisms are crucial for combating fungal infections and preventing the spread of fungal pathogens[60], [61].

Pentacyclic triterpenoids also show promising activity against parasitic organisms, including protozoa and helminths. They have demonstrated antiprotozoal effects against parasites such as Plasmodium, the causative agent of malaria, and Leishmania, responsible for leishmaniasis[62]. These compounds interfere with the survival, growth, and replication of parasites, providing potential therapeutic options for parasitic infections.

In addition to their antimicrobial activities, pentacyclic triterpenoids possess antiviral properties, making them potential agents for combating viral infections. They have been studied for their activity against a range of enveloped viruses, including influenza, herpes simplex, and human immunodeficiency virus (HIV)[63].

4.5. Other pharmacological activities:

In addition to the well-known medicinal properties of pentacyclic triterpenoids, they also exhibit a range of other pharmacological activities, including antidiabetic[64], [65], anti-obesity[66], and cardiovascular effects. These activities highlight their potential as therapeutic agents for various metabolic and cardiovascular disorders[67].

V. Ecological significance of pentacyclic triterpenoids[68], [69]:

Pentacyclic triterpenoids play essential ecological roles in both plant defense mechanisms and allelopathy. These compounds serve as integral components of plants' defense systems, acting as deterrents, repellents, and toxins against herbivores and microbial pathogens. By enhancing plant resistance, they ensure the survival and well-being of plant species in their natural habitats. Additionally, pentacyclic triterpenoids exhibit allelopathic properties, influencing the growth and behavior of neighboring plants by affecting seed germination, root growth, and nutrient uptake. These interactions shape plant community dynamics and contribute to the balance and biodiversity of natural ecosystems. Understanding the ecological significance of pentacyclic triterpenoids sheds light on their multifaceted nature beyond their therapeutic potential.

VI. CONCLUSION:

In conclusion, pentacyclic triterpenoids represent a fascinating class of natural compounds with diverse chemical structures and remarkable biological activities. Through extensive research, we have discovered their potential in various therapeutic areas, including cancer treatment, anti-inflammatory interventions, and hepatoprotection. Their wide distribution in the plant kingdom and their ecological roles in plant defense mechanisms further highlight their significance in nature. Traditional medicine practices have long recognized the medicinal properties of pentacyclic triterpenoids, providing a valuable foundation for modern drug discovery efforts. The pharmacological properties exhibited by these compounds, such as their anticancer, antioxidant, antiviral, and immunomodulatory activities, make them promising candidates for further investigation and development. As we delve deeper into the understanding of their structure-activity relationships and continue to explore their therapeutic potential, pentacyclic triterpenoids hold immense promise for the future of drug development. Continued research and exploration of these compounds

will undoubtedly unlock new insights and possibilities, paving the way for innovative treatments and sustainable pharmaceutical approaches.

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VIII. CONFLICT OF INTEREST

The authors declare no conflict of interest related to this study. The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of our affiliations.

REFERENCES:

[1] James J. T. and Dubery I. A. 2009. Pentacyclic triterpenoids from the medicinal herb, Centella asiatica (L.) Urban. Molecules (Basel, Switzerland), 14(10); 3922–3941.
[2] Perveen S. 2018. Introductory Chapter: Terpenes and Terpenoids. IntechOpen. doi: 10.5772/intechopen.79683
[3] Dinda, B., Debnath, S., Mohanta, B. C., and Harigaya, Y. 2010. Naturally occurring triterpenoid saponins. Chemistry & biodiversity, 7(10); 2327-2580.
[4] Hordyjewska, A., Ostapiuk, A., Horecka, A., and Kurzepa, J. 2019. Betulin and betulinic acid: Triterpenoids derivatives with a powerful biological potential. Phytochemistry Reviews, 18; 929-951.
[5] Singh, G. B., Singh, S., Bani, S., Gupta, B. D., and Banerjee, S. K. 1992. Anti-inflammatory activity of oleanolic acid in rats and mice. Journal of Pharmacy and Pharmacology, 44(5), 456-458.
[6] Iskender, H., Dokumacioglu, E., Terim Kapakin, K. A., Bolat, I., Mokhtare, B., Hayirli, A., and Yenice, G. 2023. Effect of Oleanolic acid administration on hepatic AMPK, SIRT-1, IL-6 and NF-κB levels in experimental diabetes. Journal of Diabetes & Metabolic Disorders, 1-10.
[7] Tang, Z. Y., Li, Y., Tang, Y. T., Ma, X. D., and Tang, Z. Y. 2022. Anticancer activity of oleanolic acid and its derivatives: Recent advances in evidence, target profiling and mechanisms of action. Biomedicine & Pharmacotherapy, 145; 112397.
[8] Zhao, L., Duan, X., Cao, W., Ren, X., Ren, G., Liu, P., and Chen, J. 2021. Effects of different drying methods on the characterization, dissolution rate and antioxidant activity of ursolic acid-loaded chitosan nanoparticles. Foods, 10(10); 2470.
[9] Luan, M., Wang, H., Wang, J., Zhang, X., Zhao, F., Liu, Z., & Meng, Q. 2022. Advances in anti-inflammatory activity, mechanism and therapeutic application of ursolic acid. Mini reviews in medicinal chemistry, 22(3); 422-436.
[10] Mlala, S., Oyedeji, A. O., Gondwe, M., and Oyedeji, O. O. 2019. Ursolic acid and its derivatives as bioactive agents. Molecules, 24(15); 2751.
[11] Khwaza, V., Oyedeji, O. O., & Aderibigbe, B. A. 2020. Ursolic acid-based derivatives as potential anti-cancer agents: An update. International journal of molecular sciences, 21(16); 5920.
[12] Lin, J. H., Chen, S. Y., Lu, C. C., Lin, J. A., & Yen, G. C. 2020. Ursolic acid promotes apoptosis, autophagy, and chemosensitivity in gemcitabine-resistant human pancreatic cancer cells. Phytotherapy Research, 34(8); 2053-2066.
[13] SHAIKH, N., SAWANT, G., & DIXIT, N. 2021. A review on ursolic acid: A naturally obtained pentacyclic triterpene. Star, 14(5); 31.
[14] Gazim, Z. C., Valle, J. S., Carvalho dos Santos, I., Rahal, I. L., Silva, G. C. C., Lopes, A. D., ... and Gonçalves, D. D. 2022. Ethnomedicinal, phytochemical and pharmacological investigations of Baccharis dracunculifolia DC.(ASTERACEAE). Frontiers in Pharmacology, 13; 1048688.
[15] Ludeña-Huaman, M. A., and Ramos-lnquiltupa, D. A. 2019. Determination of the content of ursolic and oleanolic acid in the cuticular wax of fruits of different species of Rosaceae. Revista Colombiana de Química, 48(2); 15-20.
[16] Jordamović, N., Pehlivanović, B., Nikšić, H., Gušić, I., Korić, E., Dedić, M., and Durić, K. (2023). Actividad antiproliferativa y antinflamatoria de los extractos de triterpenos de plantas pertenecientes a la familia Lamiaceae. Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas, 22(6), 864-878.
[17] Ghiulai, R., Roşca, O. J., Antal, D. S., Mioc, M., Mioc, A., Racoviceanu, R., and Şoica, C. 2020. Tetracyclic and pentacyclic triterpenes with high therapeutic efficiency in wound healing approaches. Molecules, 25(23); 5557.
[18] Hussain, M., Debnath, B., Qasim, M., Bamisile, B. S., Islam, W., Hameed, M. S., and Qiu, D. 2019. Role of saponins in plant defense against specialist herbivores. Molecules, 24(11); 2067.
[19] Armstrong, L., Merino, F. J. Z., Miguel, M. D., Lordello, A. L. L., and Miguel, O. G. 2023. Chemical Profile of Essential Oil, Extracts and Fractions of Eugenia pyriformis Cambess. And its Antioxidant, Cytotoxic and Allelopathic Activities. Brazilian Archives of Biology and Technology, 66.
[20] Shinu, P., Gupta, G. L., Sharma, M., Khan, S., Goyal, M., Nair, A. B., and Altaweel, A. A. A. 2023. Pharmacological Features of 18β-Glycyrrhetinic Acid: A Pentacyclic Triterpenoid of Therapeutic Potential. Plants, 12(5); 1086.
[21] Ads, E. N., Hassan, S. I., Rajendrasozhan, S., Hetta, M. H., Aly, S. H., & Ali, M. A. 2022. Isolation, structure elucidation and antimicrobial evaluation of natural pentacyclic triterpenoids and phytochemical investigation of different fractions of Ziziphus spina-christi (L.) stem bark using LCHRMS analysis. Molecules, 27(6); 1805.
[22] Liu, Y., Yang, L., Wang, H., & Xiong, Y. 2022. Recent Advances in Antiviral Activities of Triterpenoids. Pharmaceuticals, 15(10); 1169.
[23] Pan, F., Zhao, X., Liu, F., Luo, Z., Chen, S., Liu, Z., and Wang, L. 2023. Triterpenoids in Jujube: A Review of Composition, Content Diversity, Pharmacological Effects, Synthetic Pathway, and Variation during Domestication. Plants, 12(7); 1501.

[24] Alfaro-Almaguer, J. A., Mejía-Manzano, L. A., and González-Valdez, J. 2022. State-of-the-art and opportunities for bioactive pentacyclic triterpenes from native mexican plants. Plants, 11(17); 2184.
[25] Gastaldo, C., Lipko, A., Motsch, E., Adam, P., Schaeffer, P., and Rohmer, M. 2019. Biosynthesis of Isoprene Units in Euphorbia lathyris Laticifers vs. Other Tissues: MVA and MEP Pathways, Compartmentation and Putative Endophytic Fungi Contribution. Molecules (Basel, Switzerland), 24(23); 4322.
[26] Ghosh, S. 2020. Triterpenoids: Structural diversity, biosynthetic pathway, and bioactivity. Studies in Natural Products Chemistry, 67; 411-461.
[27] Noushahi, H. A., Khan, A. H., Noushahi, U. F., Hussain, M., Javed, T., Zafar, M., and Shu, S. 2022. Biosynthetic pathways of triterpenoids and strategies to improve their Biosynthetic Efficiency. Plant Growth Regulation, 97(3); 439-454.
[28] Gupta, A. K., Seth, K., Maheshwari, K., Baroliya, P. K., Meena, M., Kumar, A., and Vinayak, V. 2021. Biosynthesis and extraction of high-value carotenoid from algae. Frontiers in Bioscience-Landmark, 26(6); 171-190.
[29] Choi, H. S., Han, J. Y., Cheong, E. J., and Choi, Y. E. 2022. Characterization of a pentacyclic triterpene acetyltransferase involved in the biosynthesis of taraxasterol and ψ-taraxasterol acetates in lettuce. Frontiers in Plant Science, 12; 3024.
[30] Malhotra, K., and Franke, J. 2022. Cytochrome P450 monooxygenase-mediated tailoring of triterpenoids and steroids in plants. Beilstein Journal of Organic Chemistry, 18(1); 1289-1310.
[31] Kaps, A., Gwiazdoń, P., and Chodurek, E. 2021. Nanoformulations for delivery of pentacyclic triterpenoids in anticancer therapies. Molecules, 26(6); 1764.
[32] Alfaro-Almaguer, J. A., Mejía-Manzano, L. A., and González-Valdez, J. 2022. State-of-the-art and opportunities for bioactive pentacyclic triterpenes from native mexican plants. Plants, 11(17); 2184.
[33] Darme, P., Escotte-Binet, S., Cordonnier, J., Remy, S., Hubert, J., Sayagh, C., and Aubert, D. 2022. Anti-Toxoplasma gondii effect of lupane-type triterpenes from the bark of black alder (Alnus glutinosa) and identification of a potential target by reverse docking. Parasite, 29.
[34] Ji, X., Lin, S., Chen, Y., Liu, J., Yun, X., Wang, T., and Xu, H. 2020. Identification of α-Amyrin 28-Carboxylase and Glycosyltransferase from Ilex asprella and Production of Ursolic Acid 28-O-β-D-Glucopyranoside in engineered yeast. Frontiers in Plant Science, 11, 612.
[35] Shen, P., Zhou, J., Jiang, X., Ge, H., Wang, W., Yu, B., and Zhang, J. 2022. Microbial-Catalyzed Baeyer–Villiger Oxidation for 3, 4-seco-Triterpenoids as Potential HMGB1 Inhibitors. ACS omega, 7(22); 18745-18751.
[36] Wiktorowska, E., Długosz, M., and Janiszowska, W. 2010. Significant enhancement of oleanolic acid accumulation by biotic elicitors in cell suspension cultures of Calendula officinalis L. Enzyme and Microbial Technology, 46(1); 14-20.
[37] Guang-Yi, L., Gray, A. I., and Waterman, P. G. 1989. Pentacyclic triterpenes from the fruits of Rosa sterilis. Journal of Natural Products, 52(1); 162-166.
[38] Aminfar, Z., Rabiei, B., Tohidfar, M., and Mirjalili, M. H. 2019. Identification of key genes involved in the biosynthesis of triterpenic acids in the mint family. Scientific Reports, 9(1); 1-15.
[39] Moronkola, D. O., and Oladosu, I. A. 2013. Chemical Compositions of Lonchocarpus cyanescens Benth., (Fabaceae)—Case Study of Its Volatile Oils, and Two Triterpenoids. American Journal of Plant Sciences, 2013.
[40] El-Feky, A. M., and Aboulthana, W. M. 2016. Phytochemical and biochemical studies of sage (Salvia officinalis L.). Pharmaceutical and Biosciences Journal, 56-62.
[41] El-Saber Batiha, G., Magdy Beshbishy, A., El-Mleeh, A., M. Abdel-Daim, M., and Prasad Devkota, H. 2020. Traditional uses, bioactive chemical constituents, and pharmacological and toxicological activities of Glycyrrhiza glabra L.(Fabaceae). Biomolecules, 10(3); 352.
[42] Wu, H., Tang, S., Huang, Z., Zhou, Q., Zhang, P., and Chen, Z. 2016. Hepatoprotective effects and mechanisms of action of triterpenoids from lingzhi or reishi medicinal mushroom Ganoderma lucidum (Agaricomycetes) on α-amanitin-induced liver injury in mice. International Journal of Medicinal Mushrooms, 18(9).
[43] Soccol, C. R., Bissoqui, L. Y., Rodrigues, C., Rubel, R., Sella, S. R., Leifa, F., and Soccol, V. T. 2016. Pharmacological properties of biocompounds from spores of the lingzhi or reishi medicinal mushroom Ganoderma lucidum (Agaricomycetes): A review. International Journal of Medicinal Mushrooms, 18(9).
[44] Li, Y. X., Himaya, S. W. A., and Kim, S. K. 2013. Triterpenoids of marine origin as anti-cancer agents. Molecules, 18(7); 7886-7909.
[45] Pastorino, G., Cornara, L., Soares, S., Rodrigues, F., and Oliveira, M. B. P. 2018. Liquorice (Glycyrrhiza glabra): A phytochemical and pharmacological review. Phytotherapy research, 32(12); 2323-2339.
[46] Massei, K., Michel, T., Obersat, G. I., Al-Harrasi, A., and Baldovini, N. 2023. Phytochemical of Boswellia dalzielii oleo-gum resin and evaluation of its biological properties. Phytochemistry, 113751.
[47] Manu, K. A., and Kuttan, G. 2008. Ursolic acid induces apoptosis by activating p53 and caspase-3 gene expressions and suppressing NF-κB mediated activation of bcl-2 in B16F-10 melanoma cells. International immunopharmacology, 8(7); 974-981.
[48] Harun, N. H., Septama, A. W., Ahmad, W. A. N. W., and Suppian, R. 2020. Immunomodulatory effects and structure-activity relationship of botanical pentacyclic triterpenes: A review. Chinese Herbal Medicines, 12(2); 118-124.
[49] Kamble, S. M., Goyal, S. N., and Patil, C. R. 2014. Multifunctional pentacyclic triterpenoids as adjuvants in cancer chemotherapy: a review. RSC Advances, 4(63); 33370-33382.
[50] Ghante, M. H., and Jamkhande, P. G. 2019. Role of pentacyclic triterpenoids in chemoprevention and anticancer treatment: An overview on targets and underling mechanisms. Journal of pharmacopuncture, 22(2); 55.
[51] Neto, C. C. 2011. Ursolic acid and other pentacyclic triterpenoids: anticancer activities and occurrence in berries. Berries and cancer prevention, 41-49.
[52] Shanmugam, M. K., Nguyen, A. H., Kumar, A. P., Tan, B. K., and Sethi, G. 2012. Targeted inhibition of tumor proliferation, survival, and metastasis by pentacyclic triterpenoids: Potential role in prevention and therapy of cancer. Cancer letters, 320(2); 158-170.

[53] Prasannan, R., Kalesh, K. A., Shanmugam, M. K., Nachiyappan, A., Ramachandran, L., Nguyen, A. H., and Sethi, G. 2012. Key cell signaling pathways modulated by zerumbone: role in the prevention and treatment of cancer. Biochemical pharmacology, 84(10); 1268-1276.

[54] Rabi, T., Shukla, S., and Gupta, S. 2008. Betulinic acid suppresses constitutive and TNFα-induced NF-κB activation and induces apoptosis in human prostate carcinoma PC-3 cells. Molecular Carcinogenesis: Published in cooperation with the University of Texas MD Anderson Cancer Center, 47(12); 964-973.

[55] Abdullah, Khan, M. A., Ahmad, W., Ahmad, M., Adhikari, A., Ibrar, M., and Asif, M. 2022. Antioxidant, antinociceptive, anti-inflammatory, and hepatoprotective activities of pentacyclic triterpenes isolated from Ziziphus oxyphylla Edgew. Drug and Chemical Toxicology, 45(4); 1796-1807.

[56] Grace-Lynn, C., Darah, I., Chen, Y., Latha, L. Y., Jothy, S. L., and Sasidharan, S. 2012. In vitro antioxidant activity potential of lantadene A, a pentacyclic triterpenoid of Lantana plants. Molecules, 17(9); 11185-11198.

[57] Grace-Lynn, C., Chen, Y., Latha, L. Y., Kanwar, J. R., Jothy, S. L., Vijayarathna, S., and Sasidharan, S. 2012. Evaluation of the hepatoprotective effects of lantadene A, a pentacyclic triterpenoid of Lantana plants against acetaminophen-induced liver damage. Molecules, 17(12); 13937-13947.

[58] Evaristo, F. F. V., Albuquerque, M. R. J. R., dos Santos, H. S., Bandeira, P. N., Avila, F. D. N., da Silva, B. R., ... and Teixeira, E. H. 2014. Antimicrobial effect of the triterpene 3β, 6β, 16β-trihydroxylup-20 (29)-ene on planktonic cells and biofilms from Gram positive and Gram negative bacteria. BioMed Research International, 2014.

[59] Chung, P. Y., Navaratnam, P., and Chung, L. Y. 2011. Synergistic antimicrobial activity between pentacyclic triterpenoids and antibiotics against Staphylococcus aureus strains. Annals of clinical microbiology and antimicrobials, 10; 1-6.

[60] Salih, E. Y., Fyhrquist, P., Abdalla, A. M., Abdelgadir, A. Y., Kanninen, M., Sipi, M., and Ali, H. A. 2017. LC-MS/MS tandem mass spectrometry for analysis of phenolic compounds and pentacyclic triterpenes in antifungal extracts of Terminalia brownii (Fresen). Antibiotics, 6(4); 37.

[61] Shai, L. J., McGaw, L. J., Aderogba, M. A., Mdee, L. K., and Eloff, J. N. 2008. Four pentacyclic triterpenoids with antifungal and antibacterial activity from Curtisia dentata (Burm. f) CA Sm. leaves. Journal of ethnopharmacology, 119(2); 238-244.

[62] Duarte, N., Ramalhete, C., and Lourenço, L. 2019. Plant terpenoids as lead compounds against malaria and Leishmaniasis. Studies in Natural Products Chemistry, 62; 243-306.

[63] Xiao, S., Tian, Z., Wang, Y., Si, L., Zhang, L., and Zhou, D. 2018. Recent progress in the antiviral activity and mechanism study of pentacyclic triterpenoids and their derivatives. Medicinal research reviews, 38(3); 951-976.

[64] Alqahtani, A., Hamid, K., Kam, A., Wong, K. H., Abdelhak, Z., Razmovski-Naumovski, V., and Li, G. Q. (2013). The pentacyclic triterpenoids in herbal medicines and their pharmacological activities in diabetes and diabetic complications. Current Medicinal Chemistry, 20(7); 908-931.

[65] Ramírez-Espinosa, J. J., Rios, M. Y., López-Martínez, S., López-Vallejo, F., Medina-Franco, J. L., Paoli, P., and Estrada-Soto, S. (2011). Antidiabetic activity of some pentacyclic acid triterpenoids, role of PTP–1B: In vitro, in silico, and in vivo approaches. European journal of medicinal chemistry, 46(6); 2243-2251.

[66] Rao, V. S., de Melo, C. L., Queiroz, M. G. R., Lemos, T. L., Menezes, D. B., Melo, T. S., and Santos, F. A. 2011. Ursolic acid, a pentacyclic triterpene from Sambucus australis, prevents abdominal adiposity in mice fed a high-fat diet. Journal of medicinal food, 14(11); 1375-1382.

[67] Sheng, H., and Sun, H. 2011. Synthesis, biology and clinical significance of pentacyclic triterpenes: a multi-target approach to prevention and treatment of metabolic and vascular diseases. Natural product reports, 28(3); 543-593.

[68] Wang, C. M., Chen, H. T., Li, T. C., Weng, J. H., Jhan, Y. L., Lin, S. X., and Chou, C. H. 2014. The role of pentacyclic triterpenoids in the allelopathic effects of Alstonia scholaris. Journal of chemical ecology, 40; 90-98.

[69] Macías-Rubalcava, M. L., Hernández-Bautista, B. E., Jiménez-Estrada, M., Cruz-Ortega, R., and Anaya, A. L. (2007). Pentacyclic triterpenes with selective bioactivity from Sebastiania adenophora leaves, Euphorbiaceae. Journal of chemical ecology, 33; 147-156.