The Potential of Medicinal Plants with Bioactive Compounds as Antioxidants, Anti-Inflammatory and Immunomodulators: Review

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ABSTRACT

Immunity is the body's defense mechanism against infectious diseases. The immune response can be triggered by many natural factors as well as artificial factors such as infections, immunization, and external stimuli. One of the most important functions of the immune system in a healthy body is to maintain homeostasis. Immune stimulation and immune suppression are contradicted effects of the immune functions, they can be obtained and influenced by an external and/or external factor, thus the efficiency and the function of the immune system can be affected by those factors.

Immunomodulators are agents that modulate or normalize the normal function of the immune system. Recently, many types of drugs that are used as chemotherapeutic drugs to treat serious diseases such as autoimmune diseases, cancer and inflammatory diseases showed high risks of adverse side effects. The successful treatment strategy of those diseases is to obtain the best results with minimum side effects; immunomodulators derived from natural sources are the best and potential agents to replace, prevent or even reduce the expected side effects.

Bioactive compounds extracted from natural sources were found to treat and prevent inflammatory diseases and modulate the immune function. Recently, immunomodulatory characteristics of natural bioactive compounds have attracted the attention of researchers. Using different plants, fungi or algae, promising research on the immunomodulatory effects of the bioactive compounds have come to the light. Thus, in the current review, the immunomodulatory, antioxidant and anti-inflammatory activities of some common plants have been shown.
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1- Introduction

Immunity is a natural defense mechanism that can protect the body and fight against infectious diseases. Wide range of reasonable factors affect the immune system leading to its stimulation and triggering of appropriate responses such as infections, immunization, and different external stimuli (Baxter 2007). Specific immune cells of the immune system recognize any foreign antigens that can enter the body and respond by triggering an appropriate response (Jantan, Ahmad et al. 2015).

All cells in the body that can identify, recognize, and attack foreign antigens represent a part of the immune system. Not only the cells, but also the immune system includes protein signaling cytokines and receptors, different pathway molecules as well as physical and microbial barriers that protect the body from infectious invaders, namely fungi, bacteria and viruses (Parkin and Cohen 2001, Gasmi, Shanaida et al. 2023). Two categories of the immune system are well defined, innate immunity which is memory-independent and can trigger non-specific immune responses and acquired adaptive immunity which is mainly memory-dependent (Parkin and Cohen 2001, Marshall, Warrington et al. 2018). In a healthy body, internal homeostasis is maintained by the immune system. However, exogenous and endogenous factors can change the functions and efficiency of the immune system may result in immunosuppression or immunological stimulation. Several agents that can normalize or modulate the immune response have been observed and known as immunomodulators (Tanishq and Sujata).

Initiation of the inflammatory pathway

Inflammatory pathways are complex and involve multiple signaling mechanisms that are used by the body to react with the harmful stimuli, such as pathogenic organisms, damaged cells, or toxic compounds (Sahlmann and Ströbel 2016). The inflammatory pathway is started by the initiation process when immune cells recognize harmful stimuli from specific molecules of invading antigens called PAMPs (pathogen associated molecular patterns), this recognition involves pattern recognition receptors (PRRs) like Toll-like receptors (TLRs) on the cell surface of immune cells (Cicala and Morello 2023) or cytoplasmic NOD-like receptors (Mageed, Ariyadi et al. 2023). The recognition step is followed by signal transduction, Once PRRs are activated, they trigger intracellular signaling cascades resulting in common pathways include the NF-κB, MAPK, and JAK-STAT pathways (Chen, Deng et al. 2017). These pathways lead to the activation of transcription factors that promote the expression of inflammatory genes causing activation of the immune cells to release inflammatory mediators, such as cytokines (e.g., IL-6, TNF-α), chemokines, and prostaglandins (Cicala and Morello 2023). The endothelial cell lining of the blood vessels plays a crucial role in triggering suitable inflammatory response. They become activated in response to inflammatory mediators, leading to increased permeability and leukocyte adhesion (Prescott, McIntyre et al. 2001). These mediators amplify the inflammatory response and recruit more immune cells to the site of injury or infection. After the immune response is achieved and performed its function, it must be downgraded to the normal condition. The downregulation of the inflammation is an active process that involves the removal of inflammatory mediators and cells, and the restoration of tissue homeostasis (Cicala and Morello 2023) either normally or by anti-inflammatory immunomodulators.

Types of inflammatory responses

I) Acute inflammation**:** occurs and persists for a short period in the body and then subsides. However, if the inflammatory response persists for a longer period, chronic inflammation occurs. Free radicals are produced during inflammation causing elevated oxidative stress. Failure to resolve inflammation can lead to chronic inflammatory condition, apoptosis and tissue damage.

II) Chronic inflammation**:** is characterized by continuous production of free radicals with oxidative stress that cause the onset of diseases. Long-term infections and non-infectious chronic diseases such as hypertension, Alzheimer's disease, diabetes, rheumatoid arthritis, chronic kidney disease, liver cirrhosis and obesity are major sources of chronic inflammation (Zeliger 2024).

Steps of inflammation:

Vascular and Cellular Mechanisms: Under the effects of inflammatory modulators such as cytokines and histamine are released.

Cellular infiltration: The endothelial lining of the blood capillaries at the site of infection responds to the mediators leading to vasodilation which in turn leading to increased vascular permeability, allowing immune cells and proteins to exit the bloodstream and enter the affected tissue (Tiwari, Vaishnav et al. 2024). The infiltered immune cells release cytokines and other mediators that perpetuate the inflammatory response (Libby 2007, Libby 2008, Tiwari, Vaishnav et al. 2024).

Inflammation in Chronic Diseases

Atherosclerosis**:** Inflammatory mechanisms are central to the development and progression of atherosclerosis. The recruitment of leukocytes and the involvement of innate and adaptive immune responses are critical in this process (Libby 2007).

Tendinopathy**:** Inflammatory mediators such as cytokines and prostaglandins modulate changes in the extracellular matrix, affecting tendon homeostasis and repair (Millar, Murrell et al. 2017).

Inflammatory Mechanisms in Specific Conditions

Airway Diseases**:** In conditions like COPD and asthma, inflammation is driven by epithelial cell activation and macrophage response, leading to tissue remodeling and airway obstruction (Aghasafari, George et al. 2019).

Sterile Inflammation**:** Triggered by non-infectious stimuli, sterile inflammation involves stress responses and the release of DAMPs, contributing to diseases like cancer and metabolic syndromes (Rubartelli, Lotze et al. 2013).

While inflammation is a protective response, its dysregulation can lead to chronic diseases. Understanding the intricate mechanisms of inflammation, including the roles of various cells and mediators, is essential for developing targeted therapies. However, the complexity of these mechanisms poses challenges in translating this knowledge into effective treatments, as seen in conditions like tendinopathy where the role of inflammation is still debated (Millar, Murrell et al. 2017).

Immunomodulators may include chemotherapeutic compounds and monoclonal antibodies. However, those of their general usage encounter major limitations for their risky side effects. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to reduce inflammation (Sostres, Gargallo et al. 2013). However, prolonged use of NSAIDs is also associated with severe side effects such as gastrointestinal bleeding, also several COX-2 inhibitors are associated with cardiovascular problems (Harirforoosh, Asghar et al. 2013). Thus, effective, safe immunomodulatory drugs from natural sources with fewer side effects are strongly needed and recommended to replace the chemotherapeutic drugs to overcome the expected side effects to achieve successful treatment of diseases, boosting and maintaining the immune system (Gurib-Fakim 2006, Jantan, Ahmad et al. 2015, Das 2022, Alhaithloul 2023, Gasmi, Shanaida et al. 2023).

It was found that treatments of various diseases using substances derived from medicinal plants and other natural resources have been used earlier in human history and in local cultures and communities (Street and Prinsloo 2013, Abdein 2018, Venturella, Ferraro et al. 2021, Alhaithloul 2023). Nowadays, more interest was directed by the modern international communities on using immunomodulating drugs derived from natural sources for treatment many diseases (Scalbert, Manach et al. 2005, Huang, Yu et al. 2010).

Bioactive compounds of natural sources are among the substances that have immunomodulating effects, they have different effects on the immune response either suppression or stimulation. In medical fields, immunomodulators are divided into three categories, immunoadjuvants, immunostimulants, and immunosuppressants.

Secondary metabolites in plant species as anti-inflammatory

Flavonoids are a class of polyphenolic compounds that are found abundantly in plants, they are famous for their therapeutic antioxidant and anti-inflammatory properties. They inhibit pro-inflammatory enzymes and modulate cellular signaling pathways, reducing oxidative stress and inflammation (Corona-España, Garcia-Ramirez et al. 2024, Jean-Louis, Amos et al. 2024). Specific flavonoids, such as quercetin possess significant anti-inflammatory actions, including activity against a range of human cancers and cardiovascular benefits (Jean-Louis, Amos et al. 2024).

Phenolic Compounds are prevalent in plants and have been well studied for their strong anti-inflammatory effects. They are known to reduce the production of pro-inflammatory mediators and cytokines. Extracts from common beans, such as round purple beans and white kidney beans, have demonstrated anti-inflammatory efficacy by lowering nitric oxide generation and cytokine expression in macrophages (Jadhav, Ingole et al. 2024).

Alkaloids**:** Isoquinoline alkaloids, such as lycorine and narciclasine, from the Amaryllidaceae family, have shown potent anti-inflammatory effects. These compounds modulate inflammatory pathways by affecting both pro-inflammatory and anti-inflammatory factors (Nair and Van Staden 2024). Alkaloids from Pandanus amaryllifolius, such as 6E-Pandanamine, have been identified as having significant anti-inflammatory potential through in silico studies (Arrohmah, Ibtisam et al. 2023).

Triterpenes**:** those from the Lamiaceae family, have demonstrated strong anti-inflammatory activity. The triterpene fraction of Rosmarini folium, for example, showed significant inhibition of albumin denaturation, a marker of anti-inflammatory activity (Pehlivanović et al., 2023).

Other Notable Compounds**:** Thiosulfinates and polysulfides have been identified as potential anti-inflammatory agents by suppressing the NF-kB pathway, which is crucial in inflammation modulation (Corona-España, Garcia-Ramirez et al. 2024). Trimethoxy tetrahydrobenzo dioxolo isochromene (TTDI) from Commiphora madagascariensis has shown significant suppression of pro-inflammatory cytokines in both in vitro and in vivo models (Tripathi, Gupta et al. 2024).

Plant species with anti-inflammatory properties:

Lycoris radiata is notable for its alkaloids, particularly lycorine and narciclasine, which have demonstrated significant anti-inflammatory effects. These alkaloids have been shown to inhibit key inflammatory mediators such as cyclooxygenases (COX-1 and COX-2), with selective inhibition of COX-2, which is crucial in reducing inflammation without affecting gastric mucosa, a common side effect of non-selective COX inhibitors (Liu, Huang et al. 2015). Lycorine has been shown to suppress TNF-α and other cytokines like IL-4, IL-5, and IL-13 in an ovalbumin-induced asthma model, indicating its role in reducing airway inflammation by balancing Th1/Th2 cytokines (Wang, Wu et al. 2023). Narciclasine inhibits the expression of TNF-α and IL-1β in LPS-induced macrophages, reducing the production of these cytokines and other inflammatory mediators like IL-6 and COX-2 (Shen, Xu et al. 2019).

***Crinum* Species** particularly those found in South Africa, have been traditionally used for their medicinal properties, including anti-inflammatory effects. Alkaloids from Crinum species have been shown to possess significant anti-inflammatory activities in various assays, including the modulation of inflammatory pathways involving NF-κB and MAP kinases. These species are part of ongoing research efforts to explore their potential as sources of new anti-inflammatory agents

(Nair and van Staden 2022).

Galanthus cilicicus contains alkaloids such as galanthamine, which is known for its role in modulating the cholinergic anti-inflammatory pathway (CAP). This pathway involves the inhibition of pro-inflammatory cytokine release through the action of acetylcholine on the vagus nerve, providing a unique mechanism of action compared to traditional anti-inflammatory drugs. The extracts from *Galanthus cilicicus* have shown decreased leukocyte adhesion and endothelial cell interaction, further supporting their anti-inflammatory potential (Kaya, Uzun et al. 2017).

Ginger (*Zingiber officinale*) is a rhizome flowering plant that is widely used as a spice. It is characterized by its strong odor and flavored taste. It contains bioactive ingredients such as volatile oils, resins, folic acid, vitamin B6 and vitamin C. (Morakinyo, Achema et al. 2010). Ginger has been used popularly as a medicine in different countries with different cultures. It showed potent anti-inflammatory, antioxidant and immunomodulatory effects (Khaki, FATHI et al. 2009, Ali, Al-Ghamdi et al. 2020, Ayustaningwarno, Anjani et al. 2024). It was found that ginger decreased the cyclophosphamide-induced apoptosis and inflammation (Abdel-Mageed, et al. 2024).

In a study investigating the role of ginger as a protective agent against the cyclophosphamide-induced toxicity and inflammation, it showed protective effects on liver damage, spleen damage and associated deterioration of the immune system. The elevated proinflammatory INFγ, lipid peroxidation marker MDA, the liver enzyme AST, ALT and ALP, total number of leukocytes and subsequent lymphocytes as well as the histopathological architecture of the liver were greatly returned to a values comparable to normal conditions by treatment with ginger. and showed values as normal as control group; 3) the proinflammatory cytokine IL2, Casp3 in the liver and spleen tissues, neutrophil count, hemoglobin concentration and spleen tissues were also affected by the ginger and showed valuable modulation, however their values did not reach the control values (Abdel-Mageed, et al. 2024).

Truffle is a gastronome food used in the high standard food for its high content of aroma (Patel 2012, Mustafa, Angeloni et al. 2020). It was well-known and used by Romans, Greeks, ancient Egyptians and Babylonians as food and in traditional medicine (De Silva, Rapior et al. 2012, Rosa-Gruszecka, Hilszczańska et al. 2017, Abdel-Mageed, Osman et al. 2019, Mustafa, Angeloni et al. 2020). Truffle is an ascomycetous fungus a member of Tuberaceae, generally, they are growing under the soil surface (Sirag 2009, Abdel-Mageed, Osman et al. 2019). Many truffle species belong to the genus Tuber which is considered as the true truffle (Zambonelli, Iotti et al. 2015).
Truffle showed strong hypoglycemic, and hypocholestrolemic effects as well as its potent anti-inflammatory effects. Such effects were attributed to its richness with antioxidant factors such as vitamin C, B12, and D, acidic polysaccharides, folate, polyphenols, ergothioneine and fibers (De Silva et al., 2012). In a diabetic rat model, Truffle could significantly lower glucose levels and corresponding pancreatic inflammation represented by IL-1B and iNOS oxidative stress (Abdel-Mageed, Osman et al. 2019, Dawood, Sedeek et al. 2023). In LPS/IFN-γ-stimulated RAW 264.7 macrophages through modulation of the TLR4 activation, Truffle had a significant anti-inflammatory role through downregulating the production of NO, COX- 2 and iNOS leading to downregulation of inflammatory cytokines TNF-α and IL-6 mRNA expression without affecting their protein levels (Dawood, Sedeek et al. 2023). Isolated polysaccharides of Truffle showed immunomodulatory activity It also showed immunomodulatory properties (Tang, Zhu et al. 2008, Patel 2012). Due to its high content of antioxidants that act as scavengers for the peroxy radicals, it can reduce lipid peroxidation especially those species in the Asian area and Saudi Arabia and Gulf countries, and it plays a role as hepatoprotective bioactive material (Mandeel and Al-Laith 2007, Al-Laith 2010).

Fig (*Ficus carica*) is originated in the Middle East areas such as Syria, Asia Minor, and Iran, then, it spread to the Mediterranean basin countries (Mars 2001). It is one of the important edible fruits with significant commercial value that belongs to the Moraceae family (Patil and Patil 2011). The compounds found in Ficus plants include triterpenoids, oleanolic, ursolic, protocatechuic, hydroxy ursolic, and maslinic acids, as well as alkaloids, flavonoids, tannins, phenolic acids, glycosides, steroids, and saponins. These plants are also claimed to include enzymatic components such as ascorbate peroxidase, catalase, peroxidase, and phenolic compounds, flavonoids, and vitamin C, as well as non-enzymatic elements such phenolic constituents, vitamin C, and flavonoids (Chandra, Kala et al. 2023).

As a medicinal plant, *Ficus carica* has notable anti-hyperglycemic, anti-arthritic, anti-depressant, and antibacterial properties that assist in controlling blood glucose and lower the risk of arthritis. Additionally, it has a strong anthelmintic action that aids in lowering childhood parasite issues (Arun, Pavithra et al. 2023). Prenylated isoflavone derivatives were identified and shown to have strong anti-inflammatory properties because they inhibited NO generation in a recent phytochemical study on fig fruit (Liu, Zhu et al. 2018).

It has been demonstrated that the flavonoids rutin, hesperetin, and morin can effectively lower the levels of inflammatory cytokines TNF-α, IL-1β, and IL-6 in diabetic mice ; it was shown that the flavonoid quercetin inhibited the release of iNOS and TNF-α by macrophages and the secretion of IL-1β and TNF-α in RAW 2647, when exposed to bacterial LPS. Additionally, in the mouse model, quercetin decreased IL-6 and TNF-α (Ginwala, Bhavsar et al. 2019). In research conducted on human triple- negative cells, the flavone apigenin present in fig fruit suppressed immune cell activation and down- regulated TNF-α, which in turn promoted the up-regulation of IL-1α and IL-6. Apigenin is a reasonably tiny molecule that can be used to treat CNS inflammation because it has been demonstrated to pass the blood-brain barrier and reach the cerebrospinal fluid compartment (Ginwala, Bhavsar et al. 2019).

Silymarin (*Silybum marianum*) is originally from the mountains of the Mediterranean, Asia, and North African regions, but is grown today in several parts of the world (Saleh 2016). Silymarin is usually found as a standardized extract obtained from the seeds of the Milk Thistle plant *Silybum marianum* (MacDonald-Ramos, Michán et al. 2021). Chemically, silymarin is a polyphenolic flavonoid extract consisting of about 70–80% silymarin flavonolignans (silybin A, silybin B, isosilybin A, isosilybin B, silychristin, isosilychristin, silydianin, and the flavonoids taxifolin, quercetin and kaempferol) along with 20–35% fatty acids and several other polyphenolic components (Neha, Jaggi et al. 2016).

Preclinical and clinical research has demonstrated that silymarin and its flavonolignans significantly impart pro-apoptotic, antioxidant, and anti-inflammatory properties, inducing a wide range of biological and pharmacological activities, such as immunomodulation, hepatoprotection, neuroprotection, anti-diabetic, and anti-cancer properties (Wadhwa, Pahwa et al. 2022).

Based on grown cells, including immune cells and other types of cells, the anti-inflammatory capabilities of silymarin, or its primary ingredient, silibinin/silybin, have been demonstrated in various in vitro systems. It is thought that macrophages and monocytes are crucial regulators of inflammation and significant participants in the innate immune response. They are efficient innate immunity drivers that carry out phagocytosis, cause inflammation, and trigger the adaptive immune response, which resolves the inflammation and establishes hemostasis (Austermann, Roth et al. 2022), numerous studies conducted over the past two decades have shown that the protective benefits of silymarin are primarily associated with the NF-κB pathway inhibition and the downregulation of pro- inflammatory cytokines, such as TNF-α and IL-1β (Kim, Seo et al.

2013). On the other hand, SM/SB can induce transcriptional factors (e.g., Nrf2), which control the body's defense against oxidative and inflammatory stressors (Zhao, Wang et al. 2021).

It has been determined that interleukin 8 (IL-8) is a protumoral cytokine, and there is evidence that inhibiting IL-8 lowers the risk of tumor development. In general, flavonoids lower IL-8 levels. Koltai and Fliegel, 2022 demonstrated that curcumin, apigenin, and silybin might lower IL-8 levels (Koltai and Fliegel 2022).

Hibiscus sabdariffa is a shrub from the Malvaceae family (Ali, Ashraf et al. 2018). It is grown in numerous places of the world, including West Africa, South Asia (Sindi, Marshall et al. 2014), the West Indies, Jamaica, China, and the United States (Gerald, McClendon et al. 2019). It is also grown in Egypt, Saudi Arabia, Sudan, In Australia, India, Thailand, Nigeria, and Latin America, it is commonly known as Rosella, Mesta, Krajeab, Zobo, and Sorrel (Ali, Ashraf et al. 2018).

The dried HS calyx's water decoction is frequently drunk as a beverage (Müller and Franz 1992) and utilized in traditional medicine to treat pyrexia (Frank, Janßen et al. 2005, Ali, Ashraf et al. 2018), dyslipidemia, diabetes (Jiménez-Ferrer, Alarcón-Alonso et al. 2012), high blood pressure, liver diseases, ulcers, abscesses, and anemia (Ali, Ashraf et al. 2018). The fleshy HS calyces are eaten as vegetables (Jabeur, Pereira et al. 2019) and are also used to make wine, cakes, syrup, and colorants (Christian, Nair et al. 2006).

ACE1 catalytically converts angiotensin I (Ang I) to angiotensin II (Ang II), which leads to the accumulation of Ang II. Different hypertension models have shown elevated levels of inflammatory mediators as well as cellular antioxidant capacity depletion (Dange, Agarwal et al. 2014, Abdel-Rahman, Hessin et al. 2017, Abdel-Zaher, Farghaly et al. 2018). Ang II-induced activation of the angiotensin II receptor type 1 (AT1 receptor) can activate NF-κB, resulting in the production of pro-inflammatory genes (Mezzano, Aros et al. 2004, Dange, Agarwal et al. 2014). ACE1 inhibitors can reduce Ang II levels, inhibiting Ang II-induced activation of AT1 receptors. The antioxidants (Sindi, Marshall et al. 2014, Alegbe, Teralı et al. 2019) and ACE1 inhibitory (Herrera-Arellano, Miranda-Sánchez et al. 2007, Ojeda, Jiménez-Ferrer et al. 2010) properties of HS extract constituents suggest that it can decrease inflammatory reactions. HS has been shown to reduce NF-κB levels in LPS-stimulated recombinant Human hepatoma cell line (HepG2) cells (Chou, Lo et al. 2016), metabolic syndrome, and TAA-intoxicated rats (Ezzat, Salama et al. 2016).

Acacia sp., the species *Acacia nilotica* is a tannin-rich medicinal plant, that belongs to the genus Acacia with about 900 species and has great anti-viral and cytotoxic effects (Raheel, Aslam et al. 2014). The plant contains a significant quantity of terpenoids, alkaloids, polyphenols, saponins, proteins, and polypeptides (Kaur, Michael et al. 2005, Ali, Akhtar et al. 2012).

The genus *Acacia catechu* heartwood aqueous extracts are a rich source of catechin and epicatechin, and potent antioxidant activity is detected and suggested to be responsible for the anti-inflammatory, tissue protectant, analgesic, and antineoplastic activities (Stohs and Bagchi 2015). *Acacia nilotica* is nominated as a medicinal tree, and belongs to the family Mimosaceae, it is abundant in phenolic substances involving gallic acid, condensed tannin, and other substances (Bhargava, Srivastava et al. 1998).

Anti-inflammatory effect of *Acacia nilotica* subsp. Kraussiana was documented (Eldeen, Van Heerden et al. 2010). Potent anti-inflammatory, antipyretic, analgesic, antidepressant, and anticoagulant activities were found in the extracts of *Acacia modesta* (Latif, Ismail et al. 2020). An Algerian Sahara plant, *Acacia tortilis* extract, and the phenolic compounds discovered were suggested to be useful as cytotoxic and anti-inflammatory medicines (Ziani, Carocho et al. 2020). Studies showed that *Acacia confusa* heartwood extracts or derived phytocompounds are of high potential for preventing inflammatory diseases caused by increased production of reactive oxygen species (Wu, Tung et al. 2008). The pharmaceutical properties of *Acacia hydaspica* could be due to its indigenous value against inflammatory diseases (Afsar, Khan et al. 2015). *Acacia catechu* extract showed significant anti-inflammatory activity in subjects with knee osteoarthritis, it was traditionally used as an antimicrobial, anti-inflammatory, and antifungal component (Stohs and Bagchi 2015). Overproduction of nitric oxide leads to inflammatory diseases, although it is useful for several physiological functions (Guzik, Korbut et al. 2003, Sharma, Al-Omran et al. 2007). *Acacia catechu* was found to control the production of nitric oxide (Sunil, Sunitha et al. 2019).

Chili pepper (*Capsicum species*) Antioxidant and anti-inflammatory components of plants and their role in potential health function through their effect against various pathological processes have been extensively studied in recent years (Menichini, Tundis et al. 2009, Mueller, Hobiger et al. 2010). Bioactive compounds of peppers were found to have antioxidants, anti- inflammatory, and antimicrobial activities (Careaga, Fernández et al. 2003, Spiller, Alves et al. 2008, Alvarez-Parrilla, de la Rosa et al. 2011). Chilis is classified in the genus *Capsicum*, in the family Solanaceae, and its fruits are known as berries (Azlan, Sultana et al. 2022). The beneficial functions of chili peppers as anti-tumor, anti-cancer, and antioxidant were studied (Hsu and Yen 2007, Leung 2008, Malagarie-Cazenave, Olea-Herrero et al. 2009).

Raw and roasted peppers were found to have strong antioxidant activity (Hamed, Kalita et al. 2019). The significant role of chili pepper as an anti-inflammatory agent was reviewed (Villa-Rivera and Ochoa-Alejo 2020). Bioactive compounds and vitamin C found in chili peppers are of great therapeutic importance due to their anti-inflammatory activities (Azlan, Sultana et al. 2022). Bioactive compounds, like flavonoids, phenolic acids, carotenoids, and ascorbic acid were found in *Capsicum* (Deepa, Kaur et al. 2007), and antioxidant and anti-inflammatory activities were reported in these compounds (Janssens, Hursel et al. 2014), which are essential components for the human immune system building up and maintaining (Howard, Smith et al. 1994). Pepper mixed with maize flour was used to cure a common cold, chili peppers for treating infected wounds, on the feet to cure athlete's foot fungus (Bosland and Votava 2012), capsaicin is used as a medication for arthritis, and as a cream to reduce post-operative pain (Seraglio, Silva et al. 2019). *Capsicum* was used to treat parasitic infections, wound healing, rheumatism, coughs, and sore throat, chili peppers were found to have antifungal, antiviral, anti-inflammatory, and immunomodulatory actions (Badia, Spina et al. 2017, Batiha, Alqahtani et al. 2020). Phenols, capsaicinoids and ascorbic acid components which have anti-inflammatory or antioxidant properties were found to be significantly greater in *C. baccatum* fruit compared to other species of peppers (Carr and Frei 1999, Kim, Kawada et al. 2003, Antonious, Kochhar et al. 2006, Chen, Lin et al. 2006).

Conclusion

Many bioactive compounds extracted from medicinal plants are characterized by potential anti-inflammatory properties with minimum side effects. Recently, successful treatment strategies of different types of inflammatory diseases strongly depend on minimizing the expected adverse side effects of the chemotherapeutic drugs by using bioactive compounds extracted from natural plants as protective drugs or totally replacing the chemotherapeutic drugs by the natural drugs. Such strategy gives promising results in treatment of immune-based diseases.

Conflict of interests

The authors have no conflict of interest to declare.

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