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A Comprehensive Review of Phytochemistry and Ethnopharmacology of Ziziphus xylopyrus and Berberis aristata and Immunomodulatory

Poonam Kanwar[1], Jai Singh Vaghela[2]

Department of Pharmacology, Bhupal Nobles' College of Pharmacy, Bhupal Nobles' University, Udaipur, Rajasthan, India

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***Corresponding author: Poonam Kanwar (**poonam.shekhawattt@gmail.com**)**

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Abstract:

This review contains research from the past 3 decades on *Ziziphus xylopyrus* and *Berberis aristata*, both of which exhibit medicinal properties in traditional and contemporary contexts (Sharma et al., 2024). *Ziziphus xylopyrus*, also known as *Ghunta* and *Kakora*, is distributed in northwestern and southern India, including Uttar Pradesh and Bihar, as well as in Pakistan and China (Gandagule et al., 2013). Traditionally, it is used to treat diarrhoea, chest pain, stomach-ache, and is also used as a contraceptive. Similarly, *Berberis aristata*, known as Chitra in Hindi, is found in India, Sri Lanka, Bhutan, and other parts of Asia and is utilised to treat various diseases. The bark of *Ziziphus xylopyrus* contains tannins (7.2%), 7,3,4-trihydroxy flavan-3,4-diol, and oleanic acid, while *Berberis aristata* contains protoberberine alkaloids in the root bark, polyphenolic flavonoids in the flowers, and alkaloids in the bark. Studies indicate that in India, Ayurveda employs plant extracts termed '*Rasayanas*' to enhance disease resistance. Ayurvedic medicine emphasises increasing the body's natural resistance to pathogens rather than directly neutralising them. Phytoconstituents such as saponins, which are either triterpenoid or steroidal glycosides, have been identified in both *Ziziphus xylopyrus* and *Berberis aristata* and are associated with pharmacological activities including antiallergic, antiphlogistic, cytotoxic, antitumor, antiviral, immunomodulatory, antihepatotoxic, molluscicide, and antifungal effects. These plants are considered effective in treating autoimmune and metabolic diseases due to their chemically diverse, multi-target botanical profiles, which may address chronic low-grade inflammation. In particular, in the context of multi-target immunomodulatory therapies, *Ziziphus xylopyrus* and *Berberis aristata* demonstrate significant potential for the development of standardised treatments that integrate traditional ethnobotanical knowledge with modern evidence-based pharmacology.

1. Introduction

The therapeutic use of plant-derived extracts in the treatment of human health issues began in ancient times and has evolved alongside human development. numerous plant parts, like as fruits, flowers, bark, and roots, have been inspected and successfully utilized for medicinal purposes, particularly in enhancing the human immune system, although further research remains warranted (Tiwari et al., 2018). Similarly, *Ziziphus xylopyrus* and *Berberis aristata* have been studied by biomedical researchers and have demonstrated efficacy as medicinal agents, particularly as immunomodulators (Sharma et al., 2024). Nonspecific immunomodulators provide a generalized state of resistance to pathogens or tumors. If we take the example of a fungal product, cyclosporin, which selectively inhibits T lymphocyte function and is used to prevent graft rejection (Bomford, 2010). Immunomodulation now extends beyond broad immune activation or suppression, aiming for precise interventions targeting specific cell types, signaling pathways, or inflammatory mediators involved in disease processes. One of the reasons for the emergence of a diverse range of advanced immune regulation strategies is the need to enhance therapeutic efficacy and minimise adverse effects associated with non-selective immunosuppressants or cytotoxic therapies. (Xu et al., 2025). Current trends in immunomodulation address a wide spectrum of human and animal diseases, including bacterial, fungal, and viral infections, cancers, autoimmune disorders, and inflammatory conditions (Ingle et al., 2013). Drugs that modify immune responses are commonly classified as immunomodulators. Clinically, immunomodulators are categorised as (i) immunostimulants, (ii) immunosuppressants, and (iii) immunoadjuvants.

IMMUNOMODULATORS		
Immunoadjuvants	***Immunostimulants***	***Immunosuppressants***
These agents are used for enhancing vaccine efficacy and therefore, could be considered specific immune stimulants.	***These agents are inherently nonspecific in nature as they envisaged to enhance body's resistance against infection.***	***These are a structurally and functionally heterogeneous group of drugs, which are often concomitantly administered in combination regimens to treat various types of organ transplant rejection and autoimmune Diseases***

Figure 1: Category of Immunomodulators

Source: **Agarwal and Singh, 1999**

2. ***Ziziphus xylopyrus:*** *It is commonly known as Kath Ber and exhibits a range of biological activities, some of which are* antibacterial, anti-inflammatory, and wound healing. It is also used to treat respiratory discomfort. (Jena et al., 2012).

Botanical classification: *Ziziphus xylopyrus*, commonly known as Ghunta and Kakora, is associated with the 'Kingdom *Viridaeplantae*' and 'the Subkingdom Plantae'. It is divided into 'the Class *Magnoliopsida*', 'Subclass *Rosidae*', and 'Order *Rhamnales*' and is a member of the family '*Rhamnaceae*', the 'Genus *Ziziphus*', and the Species *Xylopyrus* (Modi *et al.*, 2014).

Habitats: Gandagule *et al.* mentioned in their study 'phytochemical evaluation of the leaves of *Ziziphus xylopyrus* (Retz) Willd. *Ancient science of life*', That "*Ziziphus xylopyrus* is a great in size, straggling shrub or short tree with thorns, growing up to 4 meters in height. Its fruits are round, usually three-celled (sometimes two or four), each cell containing one seed, and are generally hard and woody. This species is native to northwestern and southern India, including Uttar Pradesh and Bihar, as well as Pakistan and China" (Gandagule *et al*., 2013).

Chemical constituents: The phytoconstituents present in various parts of *Ziziphus xylopyrus*, including leaves, flowers, seeds, stem bark, and root bark, are summarised in the following table.

Table 1: Plant Parts of *Ziziphus xylopyrus* and Phytoconstituent(s)

Plant part	Phytoconstituent(s)
Leaves	'Quercetin and quercitrin'
Flowers	'E-4-hydroxy cinnamic acid, E-4-hydroxy-3-methoxy cinnamic acid, p-coumaric acid, ferulic acid, 5,7,3',4'-tetra hydroxy3-O-a-L-rhamnosyl favone: quercitrin, 5,7,3',4'-tetrahydroxy 3-O-P-D-galactosyl, hyperoside, kaempferol, 3-O-rutinoside and Rutin'
Fruit	'3,3,4-tri-O-methyl-ellagic acid, l-leucocyanidin, vitamin C, carotene, citric acid, Oleanolic acid, sucrose and reducing sugars'
Seed	'Unsaponifiable matter: sterol; insoluble mixed fatty acids: myristic, linoleic and oleic acid'
Stem bark	'Tannins, d-7,3',4'-trihydroxyfavan-3,4-diol, oleanolic acid, Cyclopeptide alkaloids: Amphibine H, Nummularine- K'
Root bark	'Kempferol-4'-methylether and Kempferol, Cyclopeptoidal alkaloid; Xylopyrine A, B, C, D, E, F, G and H, nummularine-p and sativanine-H'
Stem wood	'Triterpenoids, lupeol, betulinic acid and isoceanothic acid' (Modi et al., 2014)

Source : Modi et al., 2014

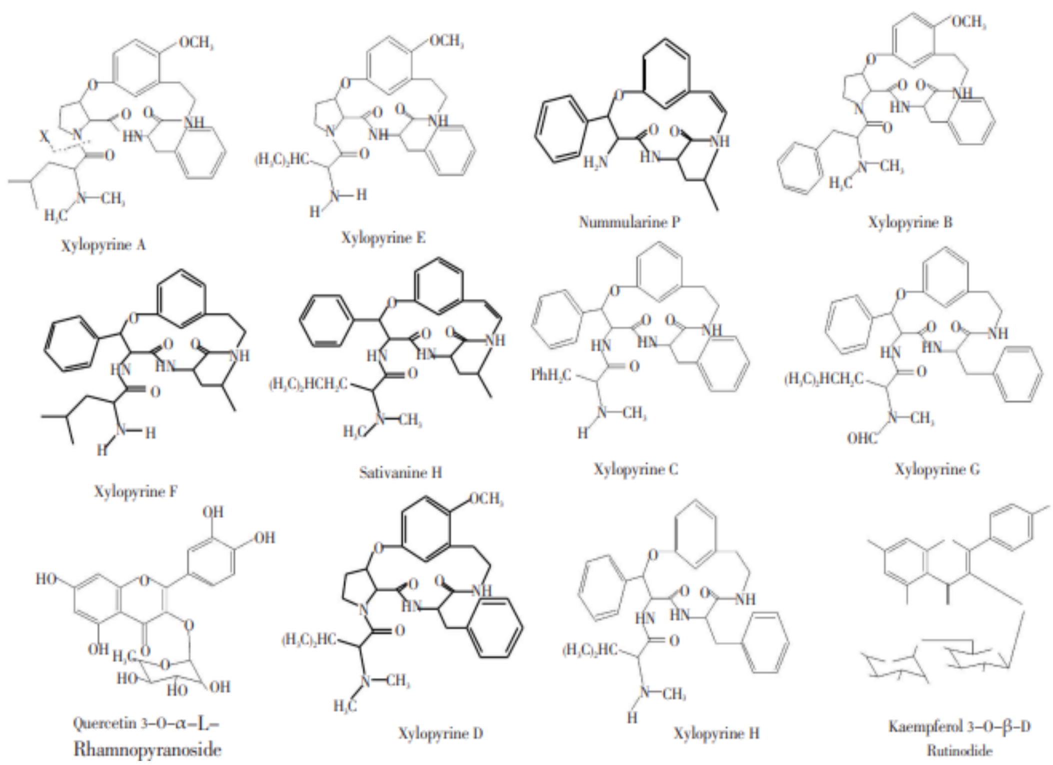


Figure 2: Ziziphus xylopyrus (Retz.) Willd. Phytoconstituents

Source : Modi *et al*., 2014

In addition to its contemporary medicinal applications, *Ziziphus xylopyrus* has a long tradition of vernacular use worldwide. In Rajasthan, India, a decoction of its fruit is used for birth control, while in Turkish medicine it serves as an effective sedative. It's powder form is used to relieve chest pain, and the seed powder form is especially useful for stomach pain. Medicinal uses and main biological activities: The bark is used to clean teeth, and a paste of the leaves is applied to treat pimples. Reports also suggest that it is used to treat diarrhea in India (Gandagule et al., 2013).

The other researchers continue to study the medicinal properties of *Ziziphus xylopyrus*. Jena et al. (2012) examined that the ethanolic extract (10%) of *Ziziphus xylopyrus* stem bark exhibited significantly greater wound healing activity compared to the control group ($p < 0.05$). Khan et al. (2022) explored the antidiabetic properties of this plant using model α-amylase and α-glucosidase enzymes and observed antidiabetic activity in *Ziziphus xylopyrus* fruit extracts. Mishra et al. (2017) evaluated the antibacterial activities of methanol and chloroform extracts of dried stem bark, determining the minimum inhibitory concentrations and zones of inhibition against 15 bacterial strains.

***Ziziphus xylopyrus* bark extract and phytochemistry**: The bark extract of *Ziziphus xylopyrus* is a rich source of bio-nutrients. The studies conducted over the past three decades have highlighted the significance of its phytochemicals (Saxena et al., 2013), as well as pharmacogenetic standards and phytochemical screening of various plant parts, including leaves at the macroscopic level (Gandagule et al.,2013). The bark contains tannins (7.2%), 7,3,4-trihydroxy flavan-3,4-diol, and oleanic acid (Yadav et al.,2011). *Ziziphus xylopyrus* is used in the treatment of pyorrhoea and to regulate oogenesis (Reddy et al., 2006). The bark is valued for its astringent properties and is used as a dental stick for cleaning teeth. Additionally, a traditional remedy involves chewing two peppers (Piper nigrum) with a two-inch piece of fresh stem bark, which is believed to cure a cough when swallowed once daily for five days (Modi et al., 2014). The plant also contains the triterpenoid lupeol, which has been structurally isolated from the stem bark and characterised by spectral data (Gandagule at. al., 2019).

3. ***Berberis aristata***: *Berberis aristata* is popularly known as Chitra in Hindi, *daruharidra in Bengali,* and similar names among common people. The two species, *Berberis aristata* and Berberis lycium, have been more popular in the traditional (Saxena et al., 2013) medicinal system. (Choudhary *et al*., 2021).

Botanical classification: The *Berberis aristata* belongs to the Plantae Kingdom, '*Phanerogamea'* is a division with *'Angiospermea'* as a Subdivision. Its Class is Dicotyledonae and Subclass is '*Polypetalae*'. The Order of this plant is '*Ranunculales'*, Family name is '*Berberidaceae*', while Genus is '*Berberis'* and Species is '*Aristata'* (Choudhary et al., 2021).

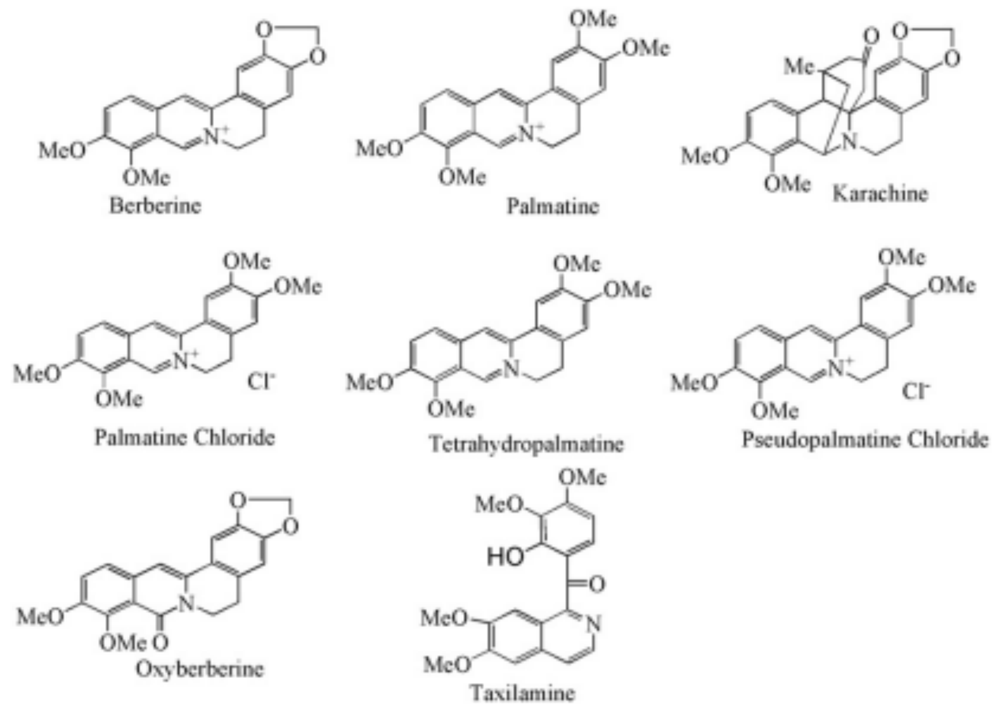
Habitats: The plant *Berberis aristata* is native to Nepal and is widely distributed across India, Sri Lanka, Bhutan, and other parts of Asia. In India, it is mostly found in the sub-Himalayan area at an altitude of 1000-3000 meters, Nilgiri hills in South India at an altitude of 1000- 2400 meters, Madhya Pradesh, Tamil Nadu, Uttar Pradesh, Himachal Pradesh, Jammu and Kashmir Uttarakhand, and Sikkim, and grows up to an altitude range between 2000 and 3500 meters(Choudhary *et al*., 2021).

Chemical constituents: The phytoconstituents of this plant for various parts, Root Bark, Flower, and Bark of *Berberis aristata* are given below in a tabular form.

Table 2: Chemical constituents of *Berberis aristata*

Plant part	Chemical class	Constituent(s)
Root Bark	Protoberberine alkaloid	Karachine, aromoline, oxyberberine, oxyacanthine, berbamine, and berberine chloride
Flower	Polyphenolic flavonoids	Quercetin, rutin, meratin and acids like Ecaffeic acid and chlorogenic acid
Bark	Alkaloids	Pakistanine, 1-O-methylpakistanine, pseudopalmatine chloride, pseudoberberine chloride, taxilamine

Source: Chemical constituents (Potdar *et al.*, 2012)



Protoberberine alkaloids from *Berberis aristata*

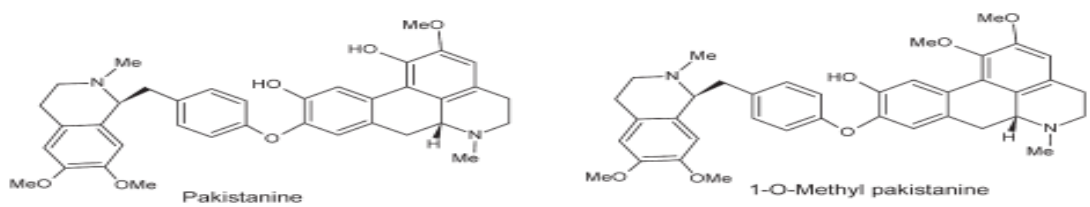


Figure 3: Chemical structure of *Berberis aristata and* important constituents (Potdar et al., 2012)

Isoquinoline alkaloids from *Berberis aristata*

Source : Potdar *et al.*, 2012

Reported biological activities of *Berberis aristata*: Malhotra *et al.* found that the use of medicinal plants is an age-old tradition, and recent use in modern therapeutics has facilitated the worldwide use of natural products for various conditions and diseases.

For the "Herbal Drug Industry", the Ethnomedicinal values of plants provide a platform for further research. *Berberis aristata has been used* since early eras to treat a variety of illnesses, including, malaria, rheumatism, jaundice, splenomegaly, conjunctivitis, and others. Scientific evidence suggests that its biological functions support its traditional use in the Orient. They highlighted the phytochemistry, distribution, synthesis, morphology,chemical reactions, nano formulation and important pharmacological properties of *Berberis aristata*. Similarly, Choudhary *et al*. *Berberis aristata*, a hard, yellow herb, has played an important role as an herbal medicine for over 2,500 years, and was even used to prevent plague in ancient Egypt. They further explain that European herbalists used this plant to treat liver and gallbladder disorders during the early Middle Ages. The *Berberis aristata* plant has been used by Russian healers and Native Americans to treat various ailments, including as a bitter tonic, stomachic, cholagogue, antiperiodic, and as a treatment for intermittent fever, neuralgia, menorrhagia, abnormal menstrual cycles, high blood pressure, and inflammation. In traditional medicine, the plant is used to treat skin diseases, menorrhagia, diarrhea, eye problems, inflammation, and wound healing. The fruit of *Berberis aristata* is considered a rich source of vitamin C. The most important formulation of this plant is 'Rashut', which acts as a tonic and blood purifier (Chaudhary et al., 2021) and is also used to treat ulcers and eye diseases. The primary functional component of the plant is berberine, which is found primarily in its roots. There are clinical reports and experimental studies that show that the plant has various medicinal properties, including antimicrobial, anti-inflammatory, analgesic, antipyretic, hepatoprotective, immunomodulator, and cardiotonic activities.

The active fraction was ethanol; its analysis revealed the presence of Phenols, Alkanes, Carboxylic acids, Methyl, carbonyl, and carbon-fluorine functional groups. Studies have shown that two acids, gallic acid and phenolic acids, i.e., p-coumaric, caffeic, and ferulic acids, are anti-inflammatory and free-radical scavengers (Shahid et al., 2010). In view of the above discussion, it is conceivable that the root parts of *Berberis aristata* have been observed to exert a significant anti-arthritic effect in experimental studies. From the present experimental findings of pharmacological parameters observed from the current investigation. The present experimental study concluded that, at a dose of 200 mg/kg, the ethanolic extract of *Berberis aristata* possesses potentially useful anti-arthritic activity, as it shows positive effects in controlling inflammation in formaldehyde-induced arthritis and an adjuvant-induced arthritis model in rats. The drug is a promising plant-derived anti-arthritic agent in the treatment of inflammatory disorders. In summary, this contemporary research provides pharmacological support for the reported folkloric use of the root parts of *Berberis aristata* in the treatment and management of painful, inflammatory arthritic conditions. So, it is that *Berberis aristata* has exceptional antibacterial and antifungal potential against clinical and standard strains and could therefore be used to derive antimicrobial agents, especially against V. cholerae, Staphylococcus species, Candida species, and Aspergillus species (sahid at. al., 2010). As *Berberis aristata* extract also exhibits anti-inflammatory, analgesic, and antipyretic properties, it could be used to isolate active components with these properties. A drug prepared from extracts of *Berberis aristata* could be an excellent drug for cholera. (Shahzad et. al., 2009)

4. Immunomodulatory Potentials, Molecular efficacy and Plant constituents

Ayurveda highlights the importance of diet, lifestyle, and medicines in preventing and treating diseases, as described in classical texts like Charaka and Sushruta Samhita.

These works emphasise how medicinal plants can help with different health conditions and introduce the idea of immunomodulation. While modern medicine has only recently started to focus on immunomodulation, some studies now refer to Ayurvedic principles (Gulati et al., 2002(30)). Ancient texts mention many plants with possible immunomodulatory effects (Singh et al., 2011; Shukla et al., 2011). For instance, Gao et al. (1989) found that water- and alkaline-soluble polysaccharides from Pinus ginseng roots and leaves contain pectins and glucans, and leaf extracts have stronger anti-complement activity. Anti-complement compounds have also been found in Jatropha multifida latex, while polymers from P. ginseng and Astragalus membranaceus show limited activation of alternative pathways (Kosasi et al., 1989). Scaglione et al. (1990) showed that P. ginseng can boost the immune system's ability to kill cells. Thabrew et al. (1991) found that water extracts of Osbeckia octandra, Melothria maderaspatana, and Phyllanthus debilis have strong, dose-dependent anticomplement effects, especially in classical pathways. Wang et al. (1991) reported that polysaccharides from Acanthopanax obovatus roots increase spleen size, spleen cell numbers, and the activity of peritoneal macrophages. Shen et al. (1991) found that polysaccharides from Acanthopanax senticosus can slow tumour growth and reduce toxic effects in animal studies.

The plant product-based new drug discoveries (Koehn & Carter, 2005) are less popular compared to synthetic drugs, as synthetic drugs are often cheaper, more efficient, and easier to regulate. The researchers have proven that natural products remain more important due to their demonstrated safety and effectiveness (Calixto, 2000; Veeresham, 2012). Progress in this field has led to new treatments for cancer, drug-resistant infections, and immune disorders (Gullo et al., 2006). More than 100 drugs from natural sources are in clinical trials, and at least 100 more are in preclinical development, showing their continued value as drug candidates (Harvey, 2008; Katiyar et al., 2012). In Ayurveda, '*Rasayanas*' are agents that boost natural resistance,(Singh at.al., 2012) a concept now recognised in modern medicine (Devasagayam & Sainis, 2002). Macrophages help regulate immune responses by engulfing foreign substances and presenting antigens to T and B cells. The research on immunomodulation focuses on specific cell types, such as T cells, which kill tumour and virus-infected cells and have diverse functions. CD8+ T cells, also called cytotoxic T cells, (33)are especially important, as are natural killer (NK) cells, which also target tumours and infected cells. B lymphocytes make antibodies against foreign proteins, and granulocytes (neutrophils, eosinophils, and basophils) help eradicate bacteria and parasites. Many medicinal plants, such as Allium sativum, Aloe vera, Andrographis paniculata, Azadirachta indica, and others, have shown immunomodulatory effects through different mechanisms (Mukherjee et al., 2014), and this leads to effects involving actions on white blood cells, macrophages, antigen-presenting cells, mast cells, natural killer cells, and co-stimulatory molecules. The Proof includes changes in white blood cell counts, allergic reactions, phagocytosis, mast cell protection, nitric oxide production, and co-stimulatory molecule expression. Some plant extracts also lower nitric oxide production and increase the expression of co-stimulatory molecules (CD40, CD80, CD86), supporting their use as immunomodulatory agents (Mukherjee *et al.,* 2014).

As immunomodulators become significant, herbal medicines have long been used to help restore and maintain health and balance in the body. This study investigates the antimicrobial and immunomodulatory effects of *Anthocephalus cadamba, particularly its effects on* cytokine induction and expression.

Rasayanas are known as rejuvenators and nutritional supplements, possessing strong antioxidant properties. They help combat oxidative stress and are primarily used for conditions such as aging, atherosclerosis, cancer, diabetes, rheumatoid arthritis, autoimmune diseases, and Parkinson's disease (Chulet & Pradhan, 2010). Rasayana herbs work by stimulating, supporting, or suppressing the immune system. Their immunomodulatory effects include increasing phagocytosis, activating macrophages, increasing peritoneal macrophages, stimulating lymphoid cells, improving immune cell function, increasing antigen-specific immunoglobulin levels, increasing nonspecific immune mediator and natural killer cell counts, reducing chemotherapy-induced leukopenia, and increasing total white cell count and interleukin-2 levels. Using plant extracts to adjust the immune response has been shown to help keep people healthy, whether they are sick or not (Haase et al., 1997). Agents that strengthen the body's defenses when the immune system is weakened can also help with standard chemotherapy (Wagner, 1984). Because bone marrow produces many cells, it is particularly sensitive to cytotoxic drugs and is most affected by immunosuppression therapy. Stem cell depletion and impaired regeneration can lead to thrombocytopenia and leukopenia (Bafna and Mishra, 2006). Plant compounds such as saponins, which are triterpenoid or steroidal glycosides, have shown various pharmacological effects, such as antiallergic, anti-inflammatory, cytotoxic, antitumor, antiviral, immunomodulating, antihepatotoxic, molluscicidal, and antifungal activities (Xiu-Feng et al., 2007).

5. Conclusion: The results of this study suggest that, due to their potent, chemically diverse, multi-target botanical compositions that can modulate chronic low-grade inflammation, both *Ziziphus xylopyrus* and *Berberis aristata* are effective in treating autoimmune and metabolic diseases. *Ziziphus xylopyrus* contains various secondary metabolites, including triterpenoids such as lupeol, betulinic acid, and isocyanothic acid, as well as macrocyclic cyclopeptide alkaloids and polyphenolics. Berberis is characterised by its unique protoberberine and secondary isoquinoline alkaloids, including berberine, berbamine, and palmatine. The mechanism of action of these plants inhibits the damaging cycle of activated macrophages and autoreactive T cells that are hallmarks of chronic autoimmune and metabolic diseases such as rheumatoid arthritis, inflammatory bowel disease, and atherosclerosis. Both of these plants have great potential to become standard therapies that combine traditional ethnobotanical knowledge with rigorous, evidence-based pharmacology, particularly for immunomodulatory disorders.

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