REVIEW ARTICLE

# Healing Potential and Therapeutic Insights of Bixa Orellana: A Holistic Review

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## Abstract

Bixa Orellana, commonly known as the annatto ,bijol or lipstick tree, is a medicinal plant with a remarkable spectrum of pharmacological activities. Rich in bioactive compounds such as bixin, norbixin, flavonoids, tocotrienols, and terpenes, it exhibits diverse therapeutic potential. Scientific studies have demonstrated its antimicrobial, antiparasitic, anti-inflammatory, antioxidant, neuropharmacological, analgesic, antinociceptive, anticonvulsant, and immunomodulatory properties. Additionally, it plays a crucial role in metabolic regulation, showing antidiabetic, antihyperlipidemic, and anti-obesity effects. Bixa Orellana also exerts hepatoprotective, nephroprotective, gastroprotective, and cardiovascular benefits, including hypotensive and platelet anti-aggregant activities. Its wound-healing, dermatoprotective, and anticancer properties further highlight its medicinal significance. Moreover, its potential in mosquito repellency, antihistamine activity, and multidrug resistance modulation underscores its versatility. While these pharmacological benefits reinforce its traditional medicinal use, further clinical studies are needed to validate its therapeutic applications and establish its role in modern medicine. This review explores the holistic potential of Bixa Orellana, emphasizing its promising contributions to healthcare and drug discovery.

**Keywords:** Bixa Orellana, bixin, pharmacological activities, antioxidant, anti-inflammatory, neuropharmacology, anticancer activity.
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## Preface

### Overview of Bixa Orellana

Medicinal plants have played a vital role in traditional medicine systems worldwide, offering a vast reservoir of bioactive compounds with therapeutic potential. Among these, Bijol, commonly known as Bixa Orellana, annatto , achiote or lipstick tree , stands out as a versatile plant with a rich history of use in ethnomedicine and various industries. Although it is native to Brazil, Bijol is a plant that thrives across South and Central America. Tropical nations including Peru, Mexico, Ecuador, Indonesia, India, Kenya, and East Africa are among those that cultivate it[1]. Although there are more species, Bixa Orellana L., which bears the name of Francisco Orellana, the first European to traverse the Amazon, is the most widespread worldwide[2].

### Botanical classification of Bixa Orellana

The height of Bixa Orellana, a small tree or shrub, ranges from 3 to 5 meters, occasionally reaching 10 meters. The short, 20–30 cm diameter trunk has dark grey bark with vertical rows of lenticels. The alternating leaves have long petioles, are pointed, green on both sides, and measure 10 to 20 cm in length and 5 to 10 cm in width[5]. Latin American nations—specifically, Peru, Brazil, and Mexico—are the primary commercial producers of Bijol, accounting for 60% of global production. Africa and Asia follow with 27% and 12% of global production, respectively[6]. At the start of the twenty-first century, it was projected that 10,000 tonnes of dried annatto seed were produced annually worldwide, of which 7,000 tonnes were traded internationally. About 4,000 tonnes of annatto seed are exported annually by Peru, whereas 5,000 tonnes are produced in Brazil, making it the leading producer. Kenya is the second-largest exporter, after Peru, with an annual export of over 1,500 tonnes of annatto seed and extracts. The Philippines, Angola, and Côte d'Ivoire are also exporters[7]. In the hottest regions of India, B. orellana has become naturalised, and the states of Orissa, Andhra Pradesh, and Maharashtra grow it to some degree for its seeds. Assam, West Bengal, Kerala, Tamil Nadu, and Karnataka are also home to it[8].

### Importance and Relevance

Annatto extract has become a widely used natural colorant in the food, cosmetics, and pharmaceutical industries due to its ability to impart vibrant hues without altering flavor. Its low toxicity and natural origin make it a preferred alternative to synthetic dyes, contributing to the growing demand for clean-label products[9]. In the food business, it is frequently utilized as a natural colorant in a variety of food formulations, such as margarine, ice cream, cheese, sausages and yogurt. Because of its abundant supply of carotenoids, the pharmaceutical and cosmetic industries also employ it[10].

The Piura tribe of the Amazon Rainforest uses tea brewed from young roots as an astringent, aphrodisiac, and to treat hepatitis, fever, diarrhoea, and skin problems. The seeds are used as an expectorant to treat gonorrhea, and in Colombia, bijol is used as an antivenin for snakebite[11].

**Table1:**The popular names of Bixa orellana in various countries[3]

| | |
|---|---|
| Brazil | Urucum, Urucu, Açafrão, Açafroa, Açafroeira-da-terr a |
| Peru and Cuba | Atole, Achiote, Bija |
| Mexico | Achiote |
| Puerto Rico | Achiote, Achote, Annatto, Bija, Santo-Domingo |
| Guyana | Bixa |
| Honduras | Analto |
| El Salvador | Guajachote |
| Venezuela | Onotto,Onotillo |
| Bolivia | Achiote, Urucu |
| Argentina | Urucu |
| Trinidad | Roucou |
| Suriname | Roucou ,Koessewee |
| United States | Annatto |

The Bixa orellana plant exhibits a wide range of pharmacological and therapeutic properties, making it a valuable natural resource in traditional and modern medicine. It demonstrates anticonvulsant, analgesic, antinociceptive, and spasmolytic activities, contributing to its effectiveness in pain management and neurological conditions. Additionally, it possesses antimicrobial, antibacterial, antifungal, and antileishmanial properties, making it useful against infections, including multidrug-resistant strains. The plant also supports metabolic health through its antidiabetic, antihyperlipidemic, and anti-obesity effects, while its antioxidant and anti-inflammatory properties aid in managing conditions such as colitis and bone loss. Furthermore, Bijol has been studied for its role in renal and hepatic protection, burn and wound healing, anti-ulcer effects, and platelet anti-aggregation. It has applications in treating gastrointestinal disorders like diarrhoea and intestinal parasitism, as well as respiratory and cardiovascular conditions, including hypotension and gonorrhea. Additional uses include promoting hair growth, aiding weight loss, improving sleep, and enhancing vitamin A activity. These diverse medicinal benefits highlight Bijol as a promising plant for further pharmacological research and therapeutic applications [Cross reference –Google scholar, Research gate].

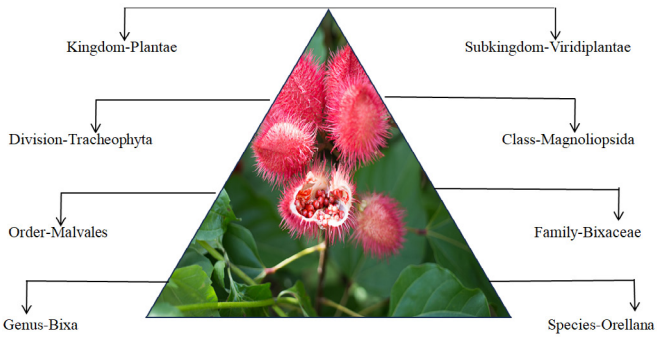


**Fig. 1:** Fruits and seeds of bixa orellana[4]

## Chemical profile

In the annatto seed coat, bixin & norbixin makes up about 70% of the pigment content[12]. Bixin was first separated from Bixa orellana seeds in 1875, and in 1961, 1H and 13C-NMR were used to fully define its chemical structure and stereochemistry. Bixin dissolves in oil and it is a diapocarotenoid that has two carboxylic acid groups, one of which is esterified. The ester group in bixin is hydrolyzed to form nor-bixin. Both of these hues are produced by the oxidative degradation of C40 carotenoids. Bixin has the chemical formula C25H30O4 (MW = 394.51) and is a 25-carbon molecule [13]. Other substances that were previously mentioned for this plant were also found, including eicosatrienoic acid, tocotrienol, and geranylgeraniol[14]. 1% of dried annatto seeds are made up of geranylgeraniol, a crucial fatty component[15] The lipid component of annatto seeds yielded tocotrienols, primarily 8-tocotrienol (140–147 mg/100 g dry seeds and 5.2–5.5% wt/wt lipid extract)[16].

Other carotenoids found in trace levels are β-carotene, cryptoxanthin, lutein, zeaxanthin, methylbixin, six apocarotenoids (C30 and C32), eight diapocarotenoids (C19, C22, C24, and C25), and a carotenoid (C14). It has also been observed that Bixa orellana is the vegetable source that contains the highest concentration of terpenes, particularly E-geranylgeraniol, which can make up as much as 57% of the dry seed's total terpene content. Geranylgeranyl formate, geranylgeranyl octadecanoic acid, and farnesylacetone are further isoprenoids that have been discovered. It also includes lipids (linoleic acid, -linolenic, and oleic acids in smaller levels), phosphate, iron, and zinc, as well as amino acids (glutamate, aspartate, and leucine). Bixin is currently the second most popular natural color in the world[18-20].

## Pharmacological activities and Therapeutic applications

### *Antibacterial and Antifungal activities*

Overall, the evidence from in vitro experiments indicates that this herbal remedy is more sensitive to Gram-negative bacteria but effective against fungi and both Gram-positive and Gram-negative bacteria[23]. When alcoholic leaf and root extracts were tested in vitro against a resistant strain of Neisseria gonorrhoeae, the results showed a notable suppression of growth. According to Ibori and Anderson (1996), the extract exclusively works against Gram-positive bacteria, specifically Enterococcus faecalis, S. aureus, and Bacillus subtilis [24]. Leaf extracts were shown to have the most activity against Bacillus pumilus, while the fungus Aspergillus niger and Candida utilis were also slightly inhibited (1–3 mm), as were the Gram-negative bacteria Serratia marcescens[25]. When tested against B. subtilis, S. aureus, Streptococcus pyogenes, Salmonella typhi, P. aeruginosa, E. coli, and nystatin for Candida albicans, ethanol extracts of B. orellana leaves and seeds showed less antibacterial efficacy than gentamicin[26].Methanol extracts from B. orellana leaves have antibacterial properties that can help cure diarrhoea

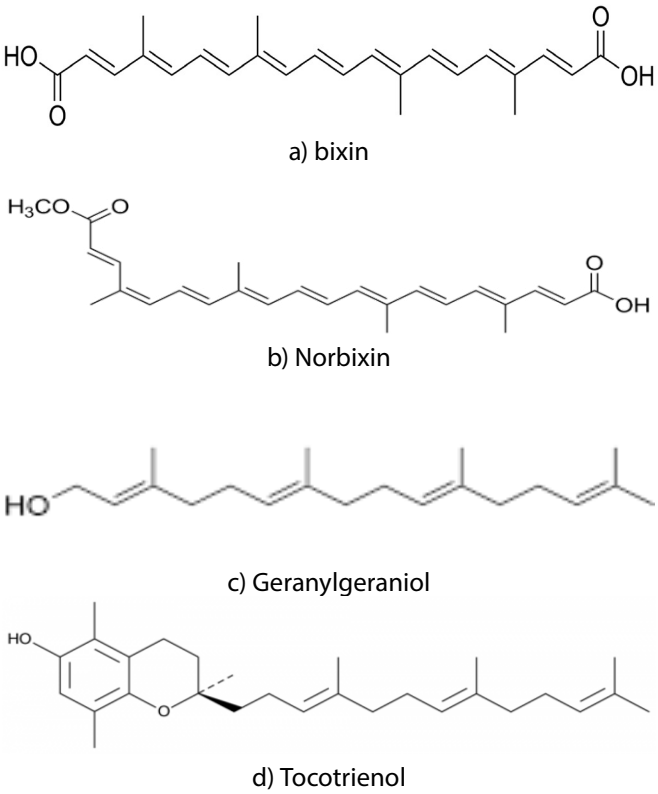


Fig. 2: a)bixin b) Norbixin c) Geranylgeraniol d) Tocotrienol[17]

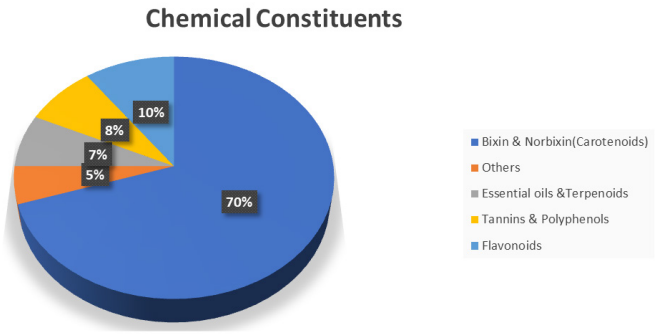


**Fig. 3:** Percentage(%) composition of the chemical constituents of Bixa Orellana[21,22]

and dysentery brought on by Shigella dysenteriae, S. aureus, and E. coli[27]. Ethanol extracts from the B. orellana plant showed antibacterial activity that inhibited both B. cereus and P. aeruginosa[28]. Furthermore, while methanolic seed extracts of B. orellana have proven superior antimicrobial activity, methanolic leaf extract of the plant also showed antibacterial activity against pathogenic bacteria [29,30]. When it comes to the examined bacteria, ethanol extracts of Bixa orellena outperform acetone extracts[31]. Ethanol extracts antifungal activity against Candida albicans at six concentrations[32]. The findings demonstrated that there were no appreciable variations in the impact of nystatin. Standard streptomycin antibiotics and phytochemicals derived from B. orellana exhibit antibacterial properties against airborne pathogens[33].Lyophilized hydroalcoholic extracts of B. orellana showed antimycobacterial activity against Mycobacterium tuberculosis, and the MIC against Salmonella typhimurium, Proteus mirabilis, B. cereus, S. aureus, and P. aeruginosa was found to be lower than that of leaf ethanol extract against Bacillus sp., S. aureus, and S. faecalis (Gram-positive microorganisms) and the fungi C. albicanse[34,35]. According to their findings, extracts from leaves and stems exhibited bacteriostatic action against the five germs. The antibacterial properties of ethanol extract were ineffective against the yeasts Cryptococcus neoformans and Candida albicans, but it demonstrated greater antimicrobial activity against Gram-positive bacteria like Bacillus sp., S. aureus, and S. faecalis than against Gram-negative bacteria like E. coli and P. aeruginosa, as well as the fungi Candida albicans and A. niger[36].

### *Antileishmanial activity*

The intracellular amastigote form of L. amazonensis was susceptible to the effects of B. orellana oil. The host cells' cytotoxic concentration was seven times more than the parasites'. Geranylgeraniol was identified as the antileishmanial component in a fairly recent research of the hexane extract of B. orellana seeds[37]. Antiparasitic action against Trypanosoma cruzi has also been demonstrated by geranylgeraniol[38]. Geranylgeraniol's antiparasitic properties have been linked to changes in mitochondrial structure, such as enlargement and the development of circular cristae. Therefore, autophagic destruction or apoptosis may result from mitochondrial injury. Furthermore, it has been demonstrated that geranylgeraniol causes kinetoplast DNA to become disorganized[39].

### *Antihelmintic activity*

Helminthic infection is a soil transmitted intestinal worm parasite that resides in the gastrointestinal tract. These endoparasites are multicellular[40].Nematodes (roundworms), Cestodes (tapeworms), and Trematodes (flatworms): The most common groups of helminths in human gut[41]. Helminth infections are referred to as helminthiasis or intestinal worm infections. In humans, some parasites are Ascaris lumbricoides (roundworm), Trichuris trichiura (whipworm), Ancylostoma duodenale and Necator americanus (hookworms), Enterobius vermicularis (pinworm), Schistosoma mansoni (blood fluke or bilharzia), Schistosoma haematobium (bladder fluke), Wuchereria bancrofti (filarial worm), Onchocerca volvulus (river blindness), Giardia lamblia, Entamoeba histolytica, Eisenia.fetida[42]. B.orellana seeds exhibited outstanding antihelmintic action against E. fetida as well[43].

### *Anti malarial activity*

B. orellana has been shown to have antimalarial action against Plasmodium gallinaceum, Plasmodium lophurae, Plasmodium falciparum, and Plasmodium berghe[44].

Utilizing hairy root culture, enough amounts of compounds ishwarane, ellagic acid, δ-tocotrienol, bixin, stigmasterol, β-sitosterol, inositol, ursolic acid, maslinic acid and arjunolic acid were produced and also tested for anti malarial activity. Stigmasterol is the most potent compound lead, other chemical constituents of B. orellana hairy roots, although had moderate antimalarial activity in 3D7 and K1 strains with low toxicity to mammalian cells during preliminary evaluation referring to other authors[45].

### *Antidermatophytic activity*

The methanolic extract's phytochemical examination identified secondary metabolites, including triterpenoids, alkaloids, flavonoids, phenols, saponins, and steroids. The found antidermatophytic activity is thought to be a result of these chemicals. In particular, the methanolic extract of young leaves was tested for antidermatophytic action against a variety of dermatophytes, such as Candida albicans, Trichophyton rubrum, Microsporum gypseum, Trichophyton tonsurans, and Trichophyton mentagrophytes. With the highest activity against Candida albicans (20.00 ± 0.00 mm inhibition zone), T. rubrum (12.66 ± 1.15 mm), M. gypseum (10.33 ± 1.15 mm), T. tonsurans (9.33 ± 0.57 mm), and T. mentagrophytes (9.00 ± 0.00 mm) were the next most active extracts[46].

## Neurological and Neuropharmacological Activities

### *Anti-convulsant activity*

The assessment of anticonvulsant activity is determining if extracts from Bixa orellana Linn. seeds or their constituents can stop or lessen seizures brought on by different experimental techniques. These techniques frequently include chemically produced convulsions, such as animal models of pentylenetetrazole (PTZ) and maximal electroshock seizures (MES). Researchers can assess Bixa orellana Linn. seeds' potential as an anticonvulsant agent by looking at how they affect seizure parameters like seizure severity, duration, and latency. Knowing the anticonvulsant properties of Bixa orellana Linn. seeds may help create new antiepileptic medications or treatments in addition to offering insights into their traditional use. Bixaorellana seed ethanolic extracts are one example of a naturally occurring chemical that shows promise as an antiepileptic medication. In both MES and PTZ models, Bixaorellana seed ethanolic extracts showed anticonvulsant efficacy, possibly via GABA A agonism, NMDA receptor antagonism, and Na+ channel inhibition[47].

### *Antinociceptive activity*

In preclinical studies, the carotenoid bixin, which is isolated from Bixa orellana seeds, has shown notable antinociceptive benefits. Bixin was demonstrated to lessen pain responses in acetic acid-induced writhing tests, formalin and hot plate tests, and investigations involving rats and mice. These effects were noted without influencing overall locomotor activity, indicating that drowsiness is not the cause of bixin's pain-relieving actions. Bixin's anti-inflammatory qualities are thought to be connected to its antinociceptive effects. Bixin has been demonstrated to reduce myeloperoxidase activity and carrageenan-induced paw edema, suggesting a decrease in neutrophil migration, a crucial element of the inflammatory response. Bixin's potential as a medicinal agent is highlighted by its dual action of decreasing pain and inflammation[48].

### *Analgesic activity*

The leaves of Bixa orellana contain a variety of bioactive substances that contribute to its analgesic effects, including tannins, steroids, alkaloids, glycosides, phenolic compounds, and saponins. Several tests, such as the acetic acid-induced writhing, hot plate, and tail immersion tests, have shown the analgesic effectiveness and considerable pain reduction results[49-51]. By using the tail immersion method, the methanolic extract of B. orellana leaves has demonstrated strong analgesic action; the highest effect was noted at a dosage of 500 mg/kg3[50]. In the abdominal contortion and hot plate models, the lyophilized aqueous extract of the leaves showed dose-dependent analgesic effects[51]. In a study comparing several extracts, Kyllinga monocephala shown a significant decrease in the number of writhes in mice, although B. orellana's methanolic extract did not. This implies that the extraction technique and plant portion employed can affect the analgesic efficacy[52]. The analgesic properties of ishwarane, a particular sesquiterpene component that was isolated from B. orellana. At greater dosages, though, it demonstrated negligible analgesic effects, suggesting that not all of B. orellana's components equally contribute to its analgesic benefits[53]. Traditionally, Bixa orellana leaf extracts have been utilized with little to no negative impact. According to animal research, there is no discernible toxicity to the extracts at doses up to 1000 mg/kg[50,54]. However, to validate these results and create safe usage guidelines, further thorough human research are required[54].

## Anti-Inflammatory and Immunomodulatory Activities

### *Anti-Inflammatory activity*

Bixin and ellagic acid are two of the chemicals that have been extracted from Bixa orellana and have shown anti-inflammatory qualities. Particularly, ellagic acid has been demonstrated to interact with the enzymes DHFR and COX2, which adds to its anti-inflammatory properties[55]. Furthermore, a recently discovered plant component called bixasteroid has demonstrated promise in preventing the generation of nitric oxide, hence bolstering its anti-inflammatory properties[56]. Bixin, a bioactive chemical included in seeds, is known to block important inflammatory pathways that are essential to the inflammatory process, including PI3K/Akt and TLR4/NF-κB[57,58]. Bixin, a bioactive chemical included in seeds, is known to block important inflammatory pathways that are essential to the inflammatory process, including PI3K/Akt and TLR4/NF-κB[58]. Extracts from the plant, especially the ethyl acetate fraction, have

been demonstrated in animal models to decrease oedema and block leukocyte migration, suggesting that they may be able to lessen inflammatory reactions[55,59,60].

### *Antihistamine activity*

In rats, it has been demonstrated that AEBO dramatically reduces peritoneal vascular permeability and paw edema brought on by histamine. Important mediators of arterial permeability, nitric oxide (NO) and vascular endothelial growth factor (VEGF), are downregulated in this impact[61]. Human umbilical vein endothelial cells (HUVEC) were used in in vitro experiments to show that AEBO inhibits histamine-induced endothelial hyperpermeability. The NO-cGMP signaling cascade, decreased intracellular calcium levels, inhibition of phospholipase C (PLC) activity, and inhibition of protein kinase C (PKC) activity are all associated with this suppression[62]. AEBO successfully restores normal endothelium barrier function by lowering histamine-mediated NO generation in endothelial cells. This reduction in NO levels is dose-dependent, with higher concentrations of AEBO showing greater inhibition[63].

### *Anticolitis activity*

Ishwarane, a sesquiterpene chemical that was discovered from Bixa orellana, has been investigated for a variety of biological properties. Ishwarane showed anti-toxic qualities at larger dosages, which may indicate possible protective effects against inflammatory disorders like colitis, even if the precise anticolitis activity was not precisely evaluated. A dose of 50 mg/kg body weight of ishwarane resulted in improved gastrointestinal motility. Given that enhanced motility might help reduce some of the symptoms of colitis, this characteristic may be helpful in managing the illness[64].

## Antioxidant and cytoprotective activities

### *Antioxidant activity*

Bixa orellana seeds have shown a high level of antioxidant activity. According to studies, the seed extracts have the same capacity to scavenge free radicals as the well-known antioxidant ascorbic acid. The extracts have significant efficacy in scavenging reactive oxygen and nitrogen species and demonstrate concentration-dependent antioxidant activity[65,66].Carotenoids such norbixin and bixin, as well as flavonoids and tocotrienols, are present and contribute to this antioxidant capacity[65,67].Bixa orellana leaves have potent antioxidant qualities as well. High concentrations of phenolic and flavonoid chemicals, which are recognized for their antioxidant properties, have been discovered in leaf extracts. These extracts have showed increased antioxidant activity compared to seed extracts in several experiments, confirming the leaves as a strong source of natural antioxidants[68,69,70].It has been noted that the essential oil extracted from Bixa orellana leaves exhibits potent antioxidant properties. Significant free radical scavenging capabilities were shown by the essential oil using techniques like ABTS and DPPH assays, confirming the plant's potential as a natural antioxidant source[71].Bixa orellana's high concentration of phenolic chemicals, flavonoids, and carotenoids is the main cause of its antioxidant activity. By effectively combating free radicals and lowering oxidative stress, these substances can aid in averting cellular damage and a number of illnesses [69,72,73].The antioxidant qualities of the essential oil are also influenced by the presence of monoterpenes and sesquiterpenes[71,73].

### *Hepatoprotective activity*

Bixa orellana's antioxidant and anti-inflammatory capabilities are the main source of its hepatoprotective qualities; extracts from the plant have been demonstrated to lower inflammatory cytokines and oxidative stress indicators, both of which are essential for minimizing liver damage[74,75]. These protective benefits are facilitated by the presence of polyphenols, saponins, tannins, and other phytochemicals in Bixa orellana[74,76].At medium to high dosages, Bixa orellana extracts can dramatically enhance liver function tests like SGPT and SGOT[76,77].Bixa orellana leaf methanolic extract was found to be especially effective at preventing liver damage brought on by carbon tetrachloride[78,79].Additionally, the aqueous extract showed notable hepatoprotective effects by lowering liver enzyme levels, especially in diabetic rats[80].

### *Renal protective activity*

Bixin has been demonstrated to lessen renal inflammation and oxidative stress. It raises the activity of antioxidant enzymes such glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) and lowers malondialdehyde (MDA) levels. This is accomplished by activating the Nrf2 pathway, which suppresses pro-inflammatory pathways including TLR4, MyD88, and NF-κB and increases the expression of antioxidant proteins such NQO1 and HO-1[77,78]. Bixin reduces kidney fibrosis by blocking the epithelial-to-mesenchymal transition (EMT) in renal tubular cells and modifying pathways such PPAR-γ/TGF-β1/Smad3. Additionally, through ubiquitination and autophagy mechanisms, it encourages the breakdown of STAT6, a crucial component of fibrosis[81-83].Bixin supplementation has been shown in studies to improve renal function by lowering serum creatinine, urea, and uric acid levels. This implies that bixin can preserve glomerular filtration rate and guard against kidney injury[81,84].

### *Vitamin A activity*

Bixa orellana seeds have been shown to have vitamin A activity. Significant vitamin A activity has been reported in the seeds' petroleum-ether extract, with levels ranging from 1,000 to 1,300 international units per gram of oil. Although several investigations did not quantitatively document the precise chemicals responsible, this activity is ascribed to the presence of molecules that resemble carotenoid[85]. Bixa orellana seeds have been shown to contain carotenoid compounds in certain research, however other investigations

have found that they lack vitamin A and carotenoids that can cause a favorable Carr-Price reaction. The carotenoid compounds present can be used as a provitamin, however, according to biological experiments conducted on rats, suggesting that they may help the body produce more vitamin A[86].

## Metabolic and Endocrine Activities

### *Antidiabetic activity (hypoglycemic and hyperglycemic)*

Bixa orellana mainly inhibits important enzymes involved in the digestion of carbohydrates, including α-amylase and α-glucosidase, to produce hypoglycemic effects. This inhibition aids in the regulation of postprandial hyperglycemia, which is essential for diabetes. Gallic acid, naringenin, and norbixin are among the plant's bioactive substances that have been found to play a major role in this action[87,88].Extracts from Bixa orellana have been shown in studies to dramatically reduce blood glucose levels in a variety of animal models. The extract lowered blood glucose levels in diabetic rats in a manner comparable to that of common antidiabetic medications like Metformin[89]. Likewise, the extract reduced fasting blood glucose levels and inhibited postprandial glucose rises in diabetic dogs[90]. Bixin, a substance derived from Bixa orellana, had notable hypoglycemic action in rats with diabetes induced by alloxan in a different investigation[88].Bixa orellana's effectiveness has been compared to that of some common antidiabetic drugs. It exhibited hypoglycemic and antihyperglycemic properties comparable to glibenclamide and acarbose, two well-known antidiabetic medications, in mouse models[91].

Bixa orellana has revealed to block important enzymes that aid in the digestion of carbohydrates, including α-amylase and α-glucosidase, which are essential for regulating postprandial hyperglycemia. Significant bioactive substances including gallic acid, naringenin, and norbixin contribute to the plant's extract's mixed and competitive inhibition of these enzymes[92,93].Bixa orellana has been shown in studies to reduce blood glucose levels in animal models of diabetes and normoglycemia. The extract may have improved peripheral glucose utilization in diabetic dogs by lowering blood glucose levels and suppressing postprandial glucose surges[94].

### *Antihyperlipidemic activity*

Aqueous extract of Bixa orellana seeds (AEBO) has been proven in studies to drastically lower triglyceride levels in hyperlipidemic models caused by ethanol, fructose, and tyloxapol. In certain animals, the extract reduced triglyceride levels by as much as 62.2%, suggesting a potent hypolipidemic impact[95].Similarly, in dyslipidemic rats, ethanolic and hexane extracts from Bixa orellana seeds have been shown to raise HDL cholesterol while decreasing triglycerides, total cholesterol, and LDL cholesterol without producing liver damage[96].

## Cardiovascular and Hematological Activities

### *Hypotensive activity*

Many bioactive substances, including as phenolic compounds, glycosides, tannins, steroids, alkaloids, and saponins, are found in Bixa orellana. These substances are thought to be involved in the plant's therapeutic qualities, including as its ability to lower blood pressure[97].According to pharmacological analysis, a water extract from Bixa orellana roots that has been partly purified exhibits strong hypotensive properties. This shows that the plant's constituents could help decrease blood pressure[98].

### *Platelet anti-aggregant activity*

Human platelet aggregation has been revealed to be inhibited by Bixa orellana. One of the plants that showed notable antiaggregant effects in a study comprising 17 distinct plant extracts that are traditionally utilized in Guatemala was Bixa orellana. This was shown in the suppression of platelet aggregation brought on by the clotting-process-inducing enzyme thrombin. Other plants that showed comparable platelet antiaggregant qualities, including Tagetes lucida, Annona reticulata, and Tridax procumbens, were also evaluated in the study. Nevertheless, among the plants studied, Bixa orellana was shown to be particularly efficient because several plant extracts in the research did not prevent platelet aggregation and even induced it in the absence of thrombin[99].

### *Antifibrinolytic activity*

Bixa orellana's leaf extract was used to test the plant's antifibrinolytic activity, and the results showed that the extract had antifibrinolytic activity within 20 seconds at a concentration of 1000 µg/mL. The extract contains a number of bioactive compounds, such as phenols, alkaloids, and flavonoids, which are probably responsible for its antifibrinolytic qualities[100].

## Gastrointestinal and Digestive Activities

### *Antiulcer activity*

Bixa orellana has been used historically to treat a number of illnesses, such as hepatitis, diarrhea, and dyslipidemia. One of the natural apocarotenoid found in Bixa orellana seeds, bixin, is what gives the plant its medicinal properties. Bixin, the main active ingredient in Bixa orellana, works therapeutically via a number of metabolic mechanisms. Because it controls the Nrf2/MyD88/TLR4 and TGF-1/PPAR-/Smad3 pathways, it has anti-inflammatory, anti-fibrotic, and antioxidant qualities[101].

### *Digestibility properties*

Mucilaginous polysaccharides, which are considered to have nutritional advantages, are found in Bixa orellana. By improving intestinal health and supplying dietary fiber, these polysaccharides may facilitate digestion[102].

### *Diarrhea treatment*

Comparing methanolic extracts of Bixa orellana seeds to the common medication Loperamide, the former showed a 75% decrease in the severity of diarrhea in mouse models, indicating strong anti-diarrheal efficacy[103]. Bixa orellana leaf hydroethanolic extracts were similarly efficient against mice's castor oil-induced diarrhea, reducing the severity of the condition by up to 87.8% at higher dosages[104]. Intestinal transit time and stool frequency were both successfully decreased by the leaf extracts. It has been demonstrated that the extracts slow down gastrointestinal transit, which lessens the symptoms of diarrhea[105].

### *Spasmolytic activity*

Extracts from Bixa orellana were successful in lessening the force of constriction that histamine caused in the ileum of isolated guinea pigs. The extract was able to neutralize the histamine-induced force of contraction by around 50% at a dosage of 10 mg/ml. Bixa orellana was contrasted with other plant extracts that exhibited spasmolytic action, including Cymbopogon citratus and Kalanchoë pinnata. Bixa orellana particularly decreased histamine-induced contractions by roughly 50% at higher doses, suggesting its potential as a moderate spasmolytic drug, whereas K. pinnata demonstrated a progressive reduction in these contractions. Bixa orellana's potential application in treating disorders involving smooth muscle spasms is suggested by its capacity to lessen histamine-induced muscular contractions. This may involve gastrointestinal conditions when it is advantageous to relax muscles[106].

### *Stomatological conditions*

Bixa orellana's dyeing qualities have led to its proposal as a possible agent for exposing dentobacterial plaque. By strengthening prevention and dental hygiene education, this application may improve oral health outcomes[107]. Although Bixa orellana extracts have been shown to be effective in treating stomatological problems, clinical validation through trials that follow best clinical standards is required before it can be widely used in dentistry services[108].

## Dermatological and Wound Healing Activities

### *Skin protection and albinism treatment*

Bixa orellana is one of the medicinal herbs commonly utilized by individuals with albinism for skin protection in the Bamako district of Mali. Its significance in traditional medicine for this community is highlighted by the fact that it is one of 19 plants that were chosen for this reason.Carotenoids, mucilages, sterols, triterpenes, and anti-free radical chemicals are among the advantageous compounds found in Bixa orellana seeds. These elements are renowned for their ability to shield the skin from harm. These substances imply that extracts from Bixa orellana can be used to create products that provide hydration, photoprotection, and general skin protection. This is especially helpful for those with albinism, who need to take better care of their skin to avoid UV damage[109].

### *Burn and wound healing*

Extracts from the leaves of Bixa orellana have demonstrated efficacy in treating burn injuries, with outcomes that are on par with those of the commercially available silver sulfadiazine (SSD). The extracts show promise as a natural treatment for burn wounds by encouraging wound contraction and re-epithelialization[110].It has been discovered that the oil extract of Bixa orellana speeds up the early stages of wound healing, including wound shrinking and epithelialization. However, as evidenced by the repaired tissue's decreased stress resistance, it can produce a scar of lesser quality than controls[111].

## Anticancer and cytotoxic activities

### *Antiproliferative activity*

The antiproliferative characteristics of B. orellana are mostly ascribed to its bioactive components, which include various phytochemicals like geranylgeraniol and carotenoids like bixin and norbixin. The cytostatic actions of the plant on tumor cells have been found to be mostly attributed to these chemicals[69,112]. Bixa orellana works against proliferation in a number of ways. By encouraging oxidative stress and amplifying the effects of chemotherapeutic drugs like dacarbazine, bixin, a key component of B. orellana, has been demonstrated to cause apoptosis and cell cycle arrest in cancer cells, including melanoma cells. This implies that bixin may play a part in combination cancer therapy treatments[113]. B. orellana has been shown to have antiproliferative effect against a variety of cancer cell lines. Research has demonstrated encouraging outcomes against human cervical cancer (HeLa), breast cancer (MCF-7), and lung cancer (A549) cells, with both crude extracts and purified bixin demonstrating notable activity[112,114].Furthermore, B. orellana seeds and leaves have demonstrated cytotoxic effects on lung cancer cell lines, with cell viability sharply declining at higher doses[100].

### *Anticancer activity*

The anticancer activities of Bixa orellana are attributed to a number of bioactive substances, including as beta-sitosterol, squalene, and geranylgeraniol. GC-MS analysis was used to identify these substances, which are well-known for their cytotoxic and apoptotic effects on cancer cells[115]. According to in silico research, bixin may increase TP53 expression while suppressing BRAF and MMP9 expression, two important targets in cancer treatment. Bixin's promise as a therapeutic agent in the treatment of skin cancer is demonstrated by its interaction with these targets, especially BRAF and SIRT3[116]. Bixin has been demonstrated to improve the efficacy of the chemotherapeutic medication dacarbazine in the treatment of melanoma. In melanoma cells, it stimulates apoptosis, decreases cell migration, enhances growth inhibition, and results in cell cycle arrest. Bixin and dacarbazine together promote lipid peroxidation and reactive oxygen species (ROS), indicating that oxidative stress is a key factor in its anticancer action[113].

*Genotoxic activity*

Bixa orellana's main carotenoid, bixin, whas demonstrated anti-genotoxic properties. In experiments with PC12 cells, bixin decreased the generation of Bixa micronuclei and DNA damage brought on by the anticancer medication cisplatin, suggesting that it may be a protective agent against drug-induced genotoxicity[117].Furthermore, bixin has been shown to make melanoma cells more sensitive to chemotherapy, which may enhance dacarbazine's protective and therapeutic actions through oxidative stress-related pathways[113].The capacity of Bixa orellana's hydro-ethanolic extract to damage DNA in bacterial strains resistant to many drugs indicates that it possesses genotoxic properties. As the first report of such genotoxic activity in B. orellana, this was demonstrated using DNA damage tests[118].On the other hand, another study discovered that Bixa orellana seed extract did not show genotoxic potential at greater dosages, indicating that genotoxic effects might vary based on the extract and the circumstances[119].

*Multidrug resistance modulation*

Significant antibacterial effectiveness against bacterial strains resistant to many drugs has been shown by Bixa orellana. The hydro-ethanolic extract of B. orellana demonstrated a minimum inhibitory concentration (MIC) between 512 and 2048 µg/mL and a zone of inhibition between 13 and 25 mm when tested against a variety of multidrug-resistant bacteria. It is noteworthy that the MIC was lowered by 2 to 10 times when ampicillin was added, suggesting a synergistic action that increases the antibiotic's effectiveness. This implies that B. orellana may heal illnesses brought on by bacteria that are resistant to treatment[118].

### Other Activities

*Mosquito repellant activity*

Several herbs, including Bixa orellana, have long been utilized by South Indian tribes to ward against mosquitoes. The cultural relevance and historical usage of B. orellana as a natural repellant are highlighted by the fact that these plants are frequently used topically as leaf juice or essential oils[120]. Extracts from the seeds of Bixa orellana have demonstrated strong mosquito-repelling properties. Specifically, anti-Aedes aegypti protection was 90% and 73% for hexane and ethanol/water extracts, respectively. This implies that B. orellana may have strong natural repellant properties. Sesquiterpenes and monoterpenes make up the majority of the volatile organic chemicals found in Bixa orellana seed extracts, with α-humulene being the most prevalent. The plant's repelling qualities are probably caused by these substances[121].

## Conclusion

This review has provided a comprehensive overview of the pharmacological properties and therapeutic potential of Bixa Orellana.By analyzing its diverse biological activities we have highlighted its significance in various therapeutic applications. Several scientific studies have demonstrated the remarkable bioactivity of Bixa orellana, highlighting its diverse pharmacological properties. These include antimicrobial and antiparasitic activities, neurological and neuropharmacological effects, anti-inflammatory and immunomodulatory properties, as well as antioxidant and cytoprotective functions. Additionally, Bixa orellana has been shown to exhibit metabolic and endocrine activities, cardiovascular and hematological benefits, and gastrointestinal and digestive effects. Furthermore, its dermatological and wound-healing potential, along with its anti-cancer and cytotoxic properties, underscore its broad therapeutic applications. These findings emphasize the significance of Bixa orellana as a promising candidate for further pharmacological and clinical investigations. *Bixa orellana* (annatto) has demonstrated significant antioxidant properties, its potential anti-clastogenic activity remains inadequately explored. Given the chromosomal abnormalities and oxidative stress associated with mutagenic disorders such as Down syndrome and Werner syndrome, Blood syndrome,Fanconi Anemia further investigation is essential to evaluate the therapeutic potential of *Bixa orellana* in these contexts.

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