

## Pharmacological and cosmeceutical applications of *Bixa Orellana* L.: A review of the scientific and patent literature

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Received 28 March 2016; Revised 30 November 2018

Medicinal plants or herbs belonging to different traditional medicinal systems have been used as therapeutic agents for curing a number of diseases and infections. Hence, the application of such traditionally known medicinal plants and its phytoconstituents have increased considerably even in modern medicines. *Bixa orellana* L. — an Indian medicinal plant which belongs to the family *Bixaceae* is an Ayurvedic herb used since ancient times. This review aims to highlight the ethnopharmacology, pharmacological and cosmeceutical uses of *B. orellana* not only from scientific literature but also from patent documents. The prior art review of the phytoconstituents shows that *B. orellana* contains a wide variety of biologically active compounds such as bixin, norbixin,  $\beta$ -carotene, lutein, tocotrienol, tocopherols, sesquiterpenes, monoterpenes, etc. Pharmacological review revealed that this plant is useful as anti-inflammatory, anti-asthma, anti-bacterial, anti-diabetic, anti-convulsant, hepatoprotective, antifungal, anticancer agent. This review also highlights the year wise patent filing trends and the major assignees active in filing patents in this area. Such a review will provide useful insights for further biological or clinical investigations of the bioactive or active fractions from the plant.

**Keywords:** Annatto, Anti-oxidant, *Bixa orellana*, Bixin, Lipstick tree, Norbixin.

**IPC code; Int. cl. (2015.01)-** A61K 36/00, A61P 3/00, A61P 31/00, A61P 39/00

### Introduction

*Bixa orellana* L. is a medicinal plant known in Ayurveda and in the traditional medicinal system of countries such as Brazil, Philippines etc. It is a therapeutically important plant commonly known as annatto plant belonging to family *Bixaceae*. It is also known for its reddish-orange dye annatto found in tropical regions across the globe.

*B. orellana* is cultivated from either seeds or branch cuttings. The plant usually grows in mountainous regions of higher elevation and lowlands areas. Apart from its medicinal use, the plant is mainly cultivated for the dye which is obtained from its seeds. This plant possesses many medicinal applications such as it aids in healing of minor wounds and burns, prevents scarring and blisters, ailments of womb or uterus, antidote to prussic acid poisoning, anti-inflammatory, asthma, pleurisy, labored breathing, astringent, bring out measles quickly, relieves stomach-ache, certain skin diseases, antipyretic and antiperiodic, cleanse from poisoning, diabetes, fevers, influenza, venereal diseases, digestive properties, diuretic, purgative, treats

gonorrhoea, treatment of jaundice, dysentery, febrifuge, shrink hemorrhoids, headaches, kidney diseases, leprosy treatment, liver trouble, snake bite, sore throat, stops nausea and vomiting, worms for children<sup>1</sup>. Scientific literature and review articles published so far provide an overview of the pharmacological actions<sup>2</sup> of *B. orellana* and its phytoconstituents. Recent literature reviews also provide insights into the different phytoconstituents from *B. Orellana* that are being used for different medicinal and cosmeceutical uses<sup>3</sup>. However, a review which particularly includes the pharmacological aspects of *B. orellana* and its bioactives as disclosed in the patent documents is not yet published. This review hence depicts an application-focused analysis wherein patents were selected because of their importance to the technical area in terms of the pharmacological and cosmeceutical applications. Such an analysis comprising of data from scientific literature, as well as patents, will be helpful to understand the evolution of the applications of traditional medicinal plants.

### Ethnopharmacology

*B. orellana* extracts from leaves, roots and seeds have traditionally been used for medicinal purposes

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by South America for treating wounds, diarrhoea and asthma<sup>4</sup>. Extracts of leaves, bark and roots are reported to be effective as antidotes for poisoning caused due to poisonous plants such as *Manihot esculenta* Crantz, *Jatropha curcas* L., and *Hura crepitans* L. In Brazil, *B. orellana* extract is used for heartburn and as a mild diuretic. The entire plant is used against fever and dysentery. Traditional healers in Colombia have also used *B. orellana* as an antivenom against snakebites. The seeds are found to be useful as an expectorant, while the roots are thought to be a digestive aid and cough suppressant. Leaf decoctions are used to treat heartburn and stomach distress, vomiting and nausea, prostate and urinary difficulties, as a mild diuretic and mild laxative, internal inflammation, cystitis, arterial hypertension, obesity, high cholesterol, and to eliminate uric acid. The methanol extract of *B. orellana* seeds illustrated hepatoprotective activity against Swiss albino rats with liver damage. *B. orellana* has been used for the treatment of diabetes mellitus. Annatto extract exhibits antimicrobial activity against *Clostridium botulinum* and *C. perfringens* strains. Amongst the natural carotenoids, bixin is one of the most effective biological singlet molecular-oxygen quenchers and hence may contribute to the protection of cells and tissues against the deleterious effects of free radicals. Bixin showed a radioprotective effect in bone marrow cells of gamma-irradiated mice. Norbixin is also found to possess antigenotoxic effects wherein it protects *Escherichia coli* cells and it also displays antimutagenic properties. The comet assay suggested that *B. orellana* shows chemo-preventive effects. Although, it has wide applications in the food industry as a colour additive it also finds application in cosmetics, textiles and pharmaceutical products. *B. orellana* has been traditionally used for face and body painting. The dye is also used to colour textiles. *B. orellana* is being used increasingly in body care products. *B. orellana* oil is rich in carotenoid content and provides antioxidant benefits when used for skin care. The dye obtained from *B. orellana* can also be used for colouring lips; hence the plant is also known as lipstick tree<sup>5</sup>.

## Materials and Methods

### Data mining

A prior art search was carried out wherein a search strategy consisting of keywords and concepts related to *B. orellana* and its biological activity in

combination with patent classification code such as the Co-operative Patent Classification (CPC) was formulated. The search was restricted to the scientific publications and patent documents published until 2013. This resulted in 194 scientific literature and 47 patent documents.

### Inclusion and exclusion criteria

The search retrieved patents and scientific literature focusing on the methods of preparing different bioactive fractions, methods of isolating the bioactives, methods of treating disorders using an extract from *B. orellana* or its phytoconstituents or pharmaceutical formulations comprising either the extract or bioactives. In order to provide a review on the pharmacological activities of *B. orellana*, only those documents focusing on the cosmeceutical as well as the therapeutic activity of *B. orellana* extract, its phytoconstituents or derivatives thereof were considered in this review. Patent documents pertaining to the isolation of bioactives, synthetic methods of preparing the bioactive derivatives etc. were excluded from this review.

## Result

The scientific literature and patent documents disclosing the pharmacological as well as cosmeceutical uses of *Bixa Orellana* extract, its bioactives or derivatives thereof were read and categorized based on its uses for treating: i) infections, ii) cancer, autoimmune and inflammatory disorders, iii) metabolic disorders, iv) as anti-oxidant, v) cosmeceutical Uses, and vi) miscellaneous uses.

Fig. 1 depicts the year wise distribution of the scientific literature and patent documents amongst the therapeutic and cosmetic applications of *B. orellana*.

The prior art review reveals that *B. orellana* and its bioactives have been extensively explored for their efficacy in treating infections caused due to bacterial or fungal species followed by its anti-oxidant activity, anti-cancer and anti-inflammatory activity and other cosmeceutical uses like anti-sunburn, anti-tanning, dermatological, hair dyeing/hair styling, anti-ageing, etc.

Fig. 2 represents the year wise distribution of scientific publications and patent documents under one of the above mentioned technical categories. The publication dates were considered for depicting the year wise publishing and patent filing activity.

The earliest scientific literature was published in 1960 while the earliest patent filings were in 1959. An increasing number of publications after 2000 indicates

that this traditional medicinal plant is being explored for its therapeutic and cosmetic uses. The decrease in the number of publications in 2013 may be due to the fact that the search was restricted to the documents published in 2013. Hence the data represented for patent filling for 2013 would be an incomplete representation, due to the time lag of 18 months required for the patents to be published online.

#### Cancer/autoimmune & inflammatory disorder

The immune system is responsible to regulate the biological mechanisms for the proper functioning of the body. However, due to the extrinsic or intrinsic factors, these biological mechanisms get deregulated leading to cancer, autoimmune diseases or inflammatory diseases. The analysis pertaining to the use of *B. orellana* for treating, autoimmune, cancer and inflammatory disorders were disclosed in 18 scientific literature and 15 patent documents.

Studies reveal that an aqueous extract of *B. orellana* leaves when administered orally at doses of 50 and 150 mg/kg for four consecutive days showed a dose-dependent inhibitory activity against bradykinin-

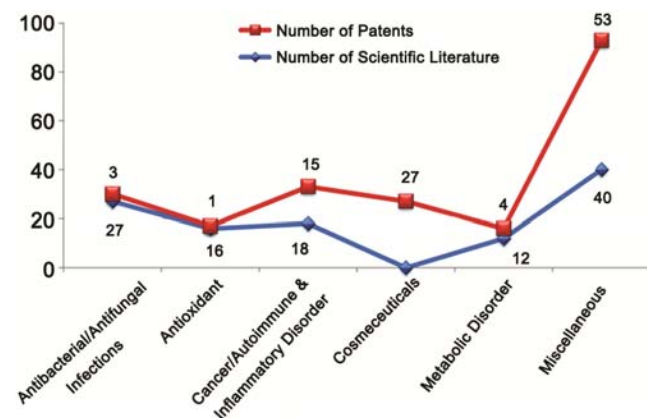


Fig. 1 — Yearwise distribution activity amongst the therapeutic and cosmetic applications

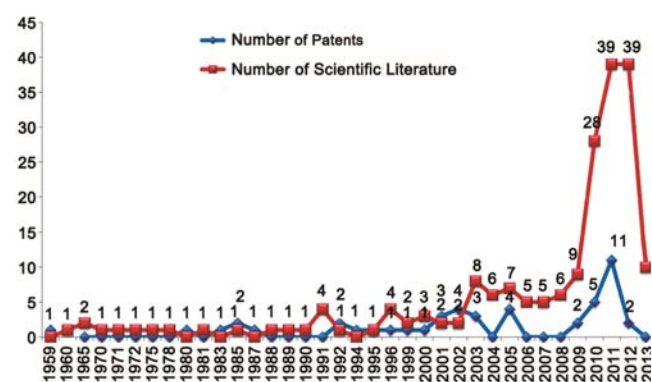


Fig. 2 — Yearwise distribution of patent and scientific literature

induced hind paw edema model, inflammatory models and bradykinin-induced increased peritoneal vascular permeability. The extract was also found to significantly suppress the nitric oxide production when administered at a dosage from 50 and 150 mg/kg<sup>6</sup>. Further, oils from seeds of *B. orellana* showed a moderate protective effect when evaluated against Swiss albino rats with a damaged liver. This hepatoprotective activity was due to its effect of lowering cholesterol and serum levels<sup>7</sup>. The methanolic extract from the seeds of *B. orellana* showed strong cytotoxic activity with LC<sub>50</sub> value of 19.3µg/m. Further studies performed using bixin which is one of the main carotenoid phytoconstituent found in the seeds of *B. orellana* showed a decrease in the viability of leukaemia K562 cells and also inhibited cell proliferation<sup>8</sup>. Further investigations pertaining to dietary supplementations comprising annatto-tocotrienols showed that it delayed the development of mammary tumours, reducing the number and size of mammary tumour masses and those of lung metastases. The studies, hence illustrate that seed extracts of *B. orellana* may comprise of bioactive phytoconstituents useful for treating tumours.

#### Metabolic Disorder

*B. orellana* extracts, bioactives or formulations comprising *B. orellana* extract as one of the ingredients of the polyherbal formulations were found to be useful in treating metabolic disorders such as diabetes or obesity-induced diabetes. The analysis reveals that there were around 12 scientific articles and around 4 patent documents which disclose the bio evaluation studies of *B. orellana* extracts or bioactives against metabolic disorders. For example, a herbal formulation comprising a methanolic extract of *B. orellana*, *Luffa acutangula* and *Kylling amonocephala* when administered to glucose loaded Swiss Webster mice as test animals showed hypoglycemic activity. Further, an infusion consisting of methanolic extracts of *B. orellana* alone was also found to lower blood glucose levels<sup>9</sup>. Studies pertaining to the use of crude annatto seed extract showed that the extract was able to lower blood glucose by primarily stimulating peripheral utilization of glucose<sup>10</sup>. Such hypoglycaemic activity was mainly contributed by the crude extracts of *B. orellana*. Evaluation of the active phytoconstituents of the seed extract revealed that geranylgeranyl octadecanoate possessed hypoglycemic activity when tested on the glycemic diabetic STZ Wistar strain in albino rats suggesting that the phytochemical

constituents stimulated the peripheral utilization of glucose, thus improving glucose uptake by adipose tissue and muscle<sup>11</sup>.

Formulations comprising *B. orellana* extract as one of the active components along with *Chrysanthemum morifolium* and *Ipomoea batatas* also inhibited lens aldose reductase activity. The active fraction from *B. orellana* extract mainly comprised of 3, 5-dicaffeoylquinic acid<sup>12</sup>. Methanolic extract of *B. orellana* leaves also inhibited Human Pancreatic Amylase (HPA) activity in a dose-dependent manner at a minimum inhibitory concentration of 49 µg/mL<sup>13</sup>.

#### Antibacterial/antifungal infections

The analysis revealed that around 22 scientific articles disclosed the bio evaluation studies pertaining to the investigation of the anti-microbial activities contributed by *B. orellana* extract. The studies related to the evaluation of anti-bacterial, anti-fungal, anti-leishmaniasis properties. For example, the ethanolic leaf extract from *B. orellana* showed a potential antibacterial effect against *Staphylococcus aureus* ATCC 25923 at a minimum inhibitory concentration of 62.5 µg/mL<sup>14</sup>. The methanolic and dimethyl sulphoxide extract from the seeds of *B. orellana* showed antibacterial activity against *Salmonella typhi* and *Staphylococcus aureus* at a concentration of about 3200 and 800 & 3200 g/mL, respectively<sup>15</sup>.

*In vitro* studies revealed that the plant extract inhibited the growth of *H. pylori*<sup>16</sup> while the leaves showed maximum activity against *Bacillus pumilus* as compared to that of the root or fruit extracts<sup>17</sup>.

Apart from anti-bacterial activity *B. orellana* also showed significant anti-leishmaniasis and anti-fungal activity. This is evident from the experimental studies which involved treating infected BALB/c mice with *B. orellana* extract. The extract was effective against amastigote and promastigote forms of *L. amazonensis*<sup>18</sup>. It also showed activity against *C. neoformans* at a minimum inhibitory concentration of about 0.078 mg/mL<sup>19</sup>.

#### Antioxidant activity

Oxidative stress or oxidative damage is one of the key elements in the development of many disorders such as diabetes, CVD related diseases, cancer, skin alignments or even immune-related disorders. The onset or progression of such disorders might also be associated with the presence of reactive oxygen species in the body or which enters into the body through food or oils. Hence, antioxidants play a major role not only

as therapeutics but also as cosmeceuticals, food preservatives or food anti-oxidants.

The analysis reveals that *B. orellana* extracts, as well as its phytoconstituents, play a vital role as antioxidants. This is evident from around 16 scientific articles and a patent document disclosing the use of *B. orellana* extracts or bioactives as anti-oxidants.

For example, alloxan-induced diabetic adult female rats were fed with standard diet while other groups received a diet with annatto extract and beta-carotene supplements. Following 30 days, the reactive oxygen species and nitric oxide species were quantified from neutrophils isolated from rats, which revealed that the production of oxygen species and nitric oxide was regulated in the rats supplemented with *B. orellana* extract<sup>20</sup>. The methanolic bark extract of *B. orellana* which contains polyphenolic, flavonoid and flavonols as the active constituents were investigated for its antioxidant activity against 1, 1-diphenyl-2-picryl hydroxyl quenching assay. The *in vitro* study revealed that the bark extract showed antiradical activity against DPPH (1, 1-diphenyl-2-picrylhydrazyl), nitric oxide and molecular oxygen, suggesting that the polyphenolic compounds were responsible for the radical scavenging activity compared to the other phytoconstituents<sup>21</sup>. On the other hand, the seeds that contain bixin as the major phytoconstituent were found to prevent chromosomal damage caused to radiation<sup>22</sup> and reduced the total number of chromosome aberrations and inhibited renal glutathione depletion caused due to cisplatin upon pretreatment with bixin<sup>23</sup>.

#### Cosmeceutical uses

Due to the antioxidant and radical scavenging properties of *B. orellana* extracts or its phytoconstituents, the medicinal plant has been extensively evaluated for its cosmeceutical properties such as UV-protecting agents, skin colour changing agent, preventing sun-tanning and anti-ageing. This is evident from the maximum number of patent filings focusing on herbal formulations containing *B. orellana* extracts or its phytoconstituents as one of the main ingredients in the cosmetic formulations. There were around 28 applicants wherein Institute of Biophytis, Koei Perfumery and Shiseido Co Ltd. were active in filing polyherbal formulations comprising active fractions from *B. orellana*. The Council of Scientific & Industrial Research, India has filed a patent application disclosing decorative plant-based aroma-therapeutic lipstick.

Other beauty care companies such as L'Oreal also has filed one patent application disclosing a photostable cosmetic composition for protecting human skin against UV radiation containing bixin. Water soluble gel type topical cosmetic formulation comprising of a combination of norbixin, bixin, carotenoids and cosmeceutically accepted additives was useful for filtering ultraviolet radiation<sup>24</sup>. On the other hand addition of *Bixa Orellana* extract to sun-tan oils was effective in preventing the tanning effect<sup>25</sup>. Food supplements comprising of norbixin and an urucum extract enriched in bixin and/or norbixin were also found to protect human skin against UV-radiation when taken orally<sup>26</sup>.

Apart from its skin-tan and UV protective nature, the phytoconstituent norbixin was also found to be an effective skin colour changing agent when taken orally<sup>27</sup>.

#### Miscellaneous

The *B. orellana* extracts also possess antiaggregant activity, antidepressant activity, prevention of retinal degeneration etc. The plant extract exhibited analgesic activity, which was experimentally verified by reduced writhing reflex in the acetic acid-induced writhing test in mice in a dose-dependent manner. The aqueous extracts also showed inhibition of human platelet aggregation induced by thrombin<sup>28</sup>. Pharmacological studies revealed that the extract produced a significant depressant effect on the voluntary activity without having an impact on the involuntary activity<sup>29</sup>. Acetone extract of annatto, bixin, and bixin derivatives exerted protective effects against tunicamycin-induced retinal damage by inhibiting an early apoptotic event and activation of caspase-3<sup>30</sup>. Guinea pig ileum induced with acetylcholine when treated with the extracts of *B. orellana* could reduce the forces of smooth muscle contraction of the ileum<sup>31</sup>. The evaluation of anti-venom property of the ethanolic extract of *B. orellana* revealed that the extract neutralized *Lachesis muta* venom and inhibited *Crotalus durissus*, *P. cumanensis* and *Micrurus mipartitus* venoms when injected intraperitoneally in mice<sup>32,33</sup>. *B. orellana* leaf extracts in non-polar solvents such as petroleum ether, ethyl acetate, diethyl ether, and n-butanol were also able to reduce convulsion in mice<sup>34</sup>.

#### Other pharmacologically important species from *Bixaceae* family

*B. orellana* belongs to the plant genus *Bixa*. Few other species from this genus include *B. arborea*, *B. excels*, *B. platycarpa*, *B. urucurana*. Further, the other genera

similar to the *Bixaceae* family include *Amoreuxia*, *Cochlospermum*, *Diegodendron*, and *Achiote*. Amongst these genera, the species such as *Cochlospermum angolense*<sup>35</sup>, *Cochlospermum planchonii*<sup>36</sup> and *Cochlospermum tinctorium*<sup>37</sup> belonging to the *Cochlospermum* genus were the only species evaluated for their biological activities such as antimalarial, anti-diabetic, hepatoprotective, antibacterial, antiviral, antiplasmodial, anti-inflammatory and anticonvulsant activity. The other species from the *Bixaceae* family can further be evaluated due to the structural similarities between the phytoconstituents and biological activity.

#### Discussion

*B. orellana* has been traditionally used as a therapeutics agent for humans in India, Brazil, Columbia and others. The traditional uses of this medicinal plant primarily were to treat infections, as an antivenin for snakebites, for heartburn, as a mild diuretic, stomach distress, vomiting and nausea. The traditional use of this a plant is well supported by scientific literature and patent documents published till date. For example, most of the publications disclose the biological evaluation of the plant extracts or its bioactives for treating various microbial infections such as bacterial infections, leishmaniasis and anti-fungal infections. On the other hand, most of the patent filings focus on the anti-oxidant property of the bioactive fractions and its applications in cosmetic formulations. Currently, it is extensively being used as a colour additive in the food industry and also finds applications in cosmetics and skin care products.

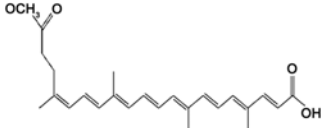
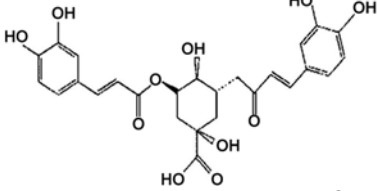
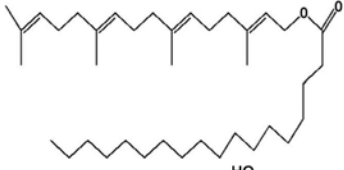
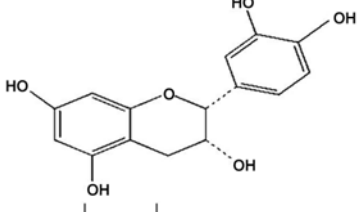
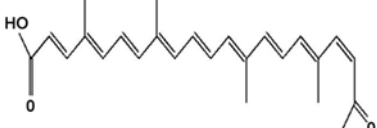
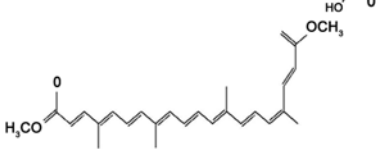
In this paper, we have reviewed the scientific literature as well as patents published until 2013. The bioactive fractions from leaf, seed and root extracts possessed potential biological activity as per the reported and published bio-evaluation investigations. Dimethyl sulphoxide and methanolic extract of *B. orellana* seeds also showed antibacterial activity against *Staphylococcus aureus* and *Salmonella typhi* while the leaves showed maximum activity against *Bacillus pumilus* as compared to that of the root or fruit extracts. *B. orellana* also showed significant anti-fungal and anti-leishmaniasis activity. This is evident from the experimental studies which involved treating infected BALB/c mice with *B. orellana* extract. The extract was effective against promastigote and amastigote forms of *L. amazonensis*<sup>18</sup>. It also showed activity against *C. neoformans* at a minimum inhibitory concentration of about 0.078 mg/mL<sup>19</sup>.

The traditional uses, as well as the biological evaluation studies as carried on different cell lines, support the therapeutic potential of *B. orellana*. However clinical studies using the crude or purified extract in human volunteers are not yet reported. The scientific literature which discloses biological investigations of the extracts either on cell lines or using animal models may serve as the potential data required for pre-clinical trials.

Apart from its use for treating infections, *Bixa Orellana* extract and bioactives have also been evaluated for its antioxidant potential. The seed and bark extracts possessed anti-oxidant activity due to its potential to scavenge free radicals wherein the extracts regulated the production of oxygen and nitric oxide species and prevented chromosomal damage caused due to ultra-violet radiations. Studies further suggest that the polyphenolic compounds were responsible for the radical scavenging activity when compared with the other phytoconstituents<sup>21</sup>.

Quantification of reactive oxygen species and nitric oxide from the neutrophils isolated from alloxan-induced diabetic adult female rats that were supplemented with a diet comprising of annatto extract and beta-carotene revealed that the production of oxygen species and nitric oxide was regulated in the rats supplemented with *Annatto* extract. These studies suggest that the bark, as well as the seed extract, contained phytoconstituents which can act as antioxidant agents. Phytochemical evaluation of these extracts reveals that carotenoids such as bixin, norbixin, lutein, zeaxanthin, dimethyl-(9Z, 9'Z)-6,6'-diapocarotene-6,6'-dioate, methyl(9'Z)-apo-6'-lycopenoate and trans-bixin are the major phytoconstituents from the seeds and seed coats<sup>38</sup>. However, amongst these carotenoids only bixin, norbixin and caffeoyl acid derivative have been evaluated for its antioxidant activity either in cell lines or in animal models. The structural details of these bioactives and activity are depicted in Table 1. The other carotenoids

Table 1 — Bio actives, their chemical structure and pharmacological uses

S. No.	Phytoconstituents	Structure	Mode of action	Cell type	Use
1.	Bixin		Inhibited cell proliferation	Leukemia K562 cells	Anticancer
2.	3,5-dicaffeoylquinic acid		Inhibit lens aldose reductase activity	---	Metabolic disorders
3.	Geranylgeranyl octadecanoate		Improving glucose uptake by adipose tissue and muscle	STZ Wistar strain in albino rats	Antidiabetic
4.	Polyphenol eg: Epicatechin		Radical scavenging activity	---	Antioxidant
5.	Norbixin		Radical scavenging activity	Human skin	Antioxidant
6.	Bixin derivatives		Inhibiting an early apoptotic event and activation of caspase-3	---	Against tunicamycin induced retinal damage

can be further evaluated as antioxidant agents. Due to the anti-oxidant activity possessed by the *B. orellana* extracts, its use in cosmetic applications has been extensively evaluated by Fast Moving Consumer Goods (FMCG) companies such as Institut Biophytis, Koei Perfumery and Shiseido Co Ltd, L'Oreal etc. Most of the evaluations with respect to the cosmeceutical applications were focused on polyherbal formulations comprising the extract or its bioactives. For example, water-soluble gel type topical cosmetic formulation comprising of a combination of norbixin, bixin, carotenoids and cosmeceutically accepted additives was found to be useful for filtering ultraviolet radiation<sup>24</sup>. On the other hand addition of *B. orellana* extract to sun-tan oils was effective in preventing the tanning effect<sup>25</sup>. Food supplements comprising of norbixin and an urucum extract enriched in bixin and/or norbixin were also found to protect human skin against UV-radiation when taken orally<sup>26</sup>. Apart from its skin-tan and UV protective nature, the phytoconstituent norbixin was also found to be an effective skin colour changing agent when taken orally<sup>27</sup>.

This review based on the existing patents and scientific literature on *B. orellana* extract or its phytoconstituents reflects the translational research of the scientific studies into the development of few *B. orellana* based product which is commercially available. Some of these commercially available products include Betacarotene and Lycopene Capsules under the brand name Laboratorios Pharmamerican Bronsol, Hydrating and Protecting Lip balm under the brand name Skin Simple, One Multi Oil with the brand name Vidivici, skin tanning or sunscreens under the brand name BronSol Beauty Line and Prönatus do Amazonas, respectively. Most of these products are cosmeceutical products reflecting the skin-tan, UV protective nature and anti-oxidant properties contributed by the *B. orellana* or its active phytoconstituents.

Studies pertaining to diabetes, cardiovascular-related diseases, cancer, skin alignments or even immune-related disorders reveal that oxidative stress or oxidative damage is one of the key elements in the development of such disorders. The reactive oxygen species present in the body or from foods or oils also contribute to the development of diseases. Hence, antioxidants play a major role not only as therapeutics but also as cosmeceuticals or as food preservatives or food antioxidants.

Further evaluation of safety parameters related to *B. orellana* and its bioactive fractions revealed that

the extract is neither genotoxic nor carcinogenic even at the highest tested concentration of about 1000 ppm when investigated for carcinogenic and anticarcinogenic effects in Wistar rat liver. *B. orellana* did not show a hepatocarcinogenic effect against DEN-induced DNA damage and preneoplastic foci in the rat liver<sup>39</sup>. The material safety data with respect to at least the major toxicity endpoints and its anti-oxidant properties provide further insights for its evaluation to be used in combination with anti-cancer or other therapeutics used for treating metabolic disorders. The seed or bark extracts can also be used as food or nutritional supplements in order to enhance the therapeutic effect of the primary drugs. Due to its good cutaneous tolerability, it can also be used as a source of natural dye for colouring applications in cosmetology<sup>40</sup>.

## Conclusion

The information provided in this review highlights that *B. orellana* extracts have not only been traditionally used but also evaluated scientifically to treat infections, metabolic disorders such as obesity, diabetes, in combination with anti-cancer drugs such as cisplatin and in cosmetic and food industry. The scientific literature and patent analysis reveal that the seed, bark, leaf and root extracts were predominantly considered for its biological investigations and properties. On the other hand, phytochemical studies reveal that there are around thirty phytoconstituents found to be present in this plant, but only a few of the bioactives such as bixin, norbixin have been studied for their biological activity in *in-vitro* or animal models. The analysis hence reveals that the other structurally potent bioactives can be further evaluated to explore the biological uses of this important medicinal traditional plant. With respect to the pharmacological activity, studies pertaining to potential therapeutic targets which are being regulated by the extract or bioactives can be explored or predicted to understand its mode of actions for optimizing its therapeutic potential.

## Conflicting interests

The authors declare no competing financial interest.

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