Review Article

Ethno-Medicinal and Therapeutic Applications of Natural Anthraquinones: Recent Trends and Advancements

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Traditional and ethno-medicinal use of plants enforces a holistic approach towards human health by wittily utilizing the synergistic potency of the bioactive compounds. Quinones are unique molecules with several therapeutic properties that lead them as most vital compound in pharmaceutical system. They can easily undergo reduction reaction paving the path for many biological processing. This class of molecules helps in treatment of several chronic ailments. Many of the drugs in Ayurvedic formulations and/or modern medicinal sectors are having one or more types of quinone groups as a major bio-active compound. However these aforementioned properties of quinones make them unique and versatile. The biochemical knowledge of these compounds is necessary to understand their physiological and toxicological properties. Amongst all quinones found naturally, anthraquinones are one of its kinds due to wide spectrum utilization in several drug formulations. In this review a brief detail of six unique yet ethno-botanically and pharmacologically versatile quinone compounds are depicted with their natural resources, structural characterization and ethno-pharmacological activities. The gathered information regarding the above mentioned bio-active compounds would be helpful in identification and isolation of these compounds from a wide range of natural sources with structural characterization and pharmacological potency. These data would be pivotal in their precise identification for further use in both Ayurvedic and modern drug formulation sectors thereby lessening the threat status of the frequently used rare, endangered and threatened plants.

Key words: Anthraquinones, plant secondary metabolites, bio-active compound, therapeutic use

The plant based compounds are widely used as complementary alternative medicines for regulating several chronic ailments. Natural bio-active compounds, mostly the plant secondary metabolites, play a key role in preparation of several drug formulations[1,2]. Medicinal plants contain several natural bio-active compounds having therapeutic potency that can act as precursors in synthesis of several drug formulations[3]. These plant components are mostly utilized in its own defence mechanism and due to their toxic nature[4], used for protection against infections or infestations[5-7]. Ethno-botanical knowledge has given an adequate basis for further investigation of medicinal properties in traditionally used plants which lead to far-flung accelerated use of natural compound[8]. Many of the bio-active compounds are still unknown to us. Only very few have been identified, isolated and some of their medicinal properties have been studied. With the current decline in the number of new molecular entities, novel bio-active compounds are being sought from medicinal plants of natural origin.

Over exploitation of specific bio-active compound to mitigate market need of drug formulation has literally created havoc and to surpass that many adulterants are being utilized as substitutes to the concerned medicinal flora with less or sometimes no efficacy. This lead to major chaos in clinical organization and diverted the concern of scientists to discover more such novel natural compounds or to produce several synthetic analogue compounds with

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higher efficacy. Development in medicinal fraternity has paved the path in discovery of many such natural products with greater therapeutic value[9]. Natural products are being used as precursor of drugs since ancient times. Diverse structural formation of each compound, make them unique from each other and it also has a vital role in each one's diverse biological functioning[10]. However identification and isolation of these compounds still remains a critical factor to known their efficacy[11].

Amongst various natural bioactive compounds available worldwide, Quinones are ubiquitous in nature and are one of the largest class of oxidized derivatives of particularly aromatic compounds[12]. The biochemistry of quinones is of particular interest because of its involvement in the electron and hydrogen transfer reactions in various biological energy conversion reactions. Some of the natural plant-derived quinones are emodin, juglone, shikonin, thymoquinone, embelin, rapanone, alizarin, chloranil, plumbagin, lapachol, ubiquinone, Thymoquinone, 5-Ipdoisatin etc[13-16]. A detailed structural elucidation along with the information regarding the source plant and their ethno-pharamacological activities are delineated here.

TYPES OF QUINONES

Considering the structure of quinones, they comprised of an unsaturated benzene ring with two oxygen atoms attached as carbonyl groups. Depending upon positioning of atoms, these can be sub-classified as 1,4-benzoquinone, 1,2-benzoquinone, 1,4-naphthoquinone and 9,10-anthraquinone[17]. Quinones are basically consists of four classes of compounds *viz.* benzoquinones, anthraquinones, naphthoquinones and isoprenoid quinones (fig. 1) having more diverse biological activities[18].

Benzoquinones:

Benzoquinone ($C_6H_4O_2$) is a cyclic conjugated diketone group, commonly known as 1,4-benzoquinone or p-benzoquinone.

Anthraquinones:

Anthraquinones ($C_{14}H_8O_2$) are type of polycyclic aromatic hydrocarbons, commonly known as 9,10-anthraquinone.

Naphthoquinones:

These contain naphthalene nucleus with carbonyl groups. Structurally these are bicyclic in nature.

Isoprenoid quinones:

These consist of a polar head and a hydrophobic side chain.

BIOCHEMISTRY OF QUINONES

The natural quinones are generally produced by the intermediate pathways of Acetate-Malonate and Shikimate Pathways[19]. Quinones have basic aromatic skeleton with several functional groups attached at different positions[20]. Parental quinone groups have the ability to add on several groups at 1,4-positions[21]. Quinones play vital role in the biochemical economy of living cells, particularly as redox-active cofactors such as plastoquinones, ubiquinones and vitamin C[12]. They can occur in a variety of forms, including monocyclic, extended or condensed form. These are oxidants, electrophiles and coloured[12] and play a pivotal role in biological functions, such as oxidative phosphorylation, electron transfer system. Quinones have several phyto-pharmacological properties like anti-parasitic, antitumor, antioxidant, antimicrobial activities[22]. These compounds show effective neurological, antithelmic, antiplasmodial activity. These are ubiquitously present with a myriad array of biological functions[23].

ANTHRAQUINONES

Anthraquinones are based on anthracene with a total of 3 benzene rings attached with each other. Each apex of the central ring is connected to a carbonyl group[24]. These are also known as anthracenedione. There are more than 700 types of anthraquinones found in plants along with some groups of fungi and lichens[25]. Till now 79 naturally occurring anthraquinones have been identified, isolated and characterized[26]. Anthraquinones like emodin, physcion, alizarin, catenarin, quinizarin, purpurin, obtusifolin (fig. 2) are synthesized *via* polyketide pathway or the shikimate pathway.

Natural source of anthraquinones:

Quinones are widely distributed in the plant kingdom and mainly exist in higher plants, such as those from Polygonaceae, Rubiaceae[27,28], Myrsinaceae[15,16,29], Leguminosae[30], Rhamnaceae, Labiatae and Boraginaceae, Plumbaginaceae, Avicenniaceae, Euphorbiaceae families, among others[31]. Some natural sources of selective anthraquinones are given in (Table 1, fig. 3).

Some natural anthraquinone compounds:

Quinones are mostly found in plants, fungi and bacteria. In angiosperms different types of quinines (biogenetically related) may occur even in the same plant[32]. Some of common natural anthraquinones are emodin, physcion, alizarin, catenarin, quinizarin, purpurin, obtusifolin, citreorosein, rhein and many more. Many studies have been done till now on anthraquinones structure, isolation, characterization and biological functions. The bibliometric analysis depicts a total publication of papers under "anthraquinone phytochemical uses" in the ScienceDirect database. The trend of research in this domain has extensively increased in the last 10 y (fig. 4).

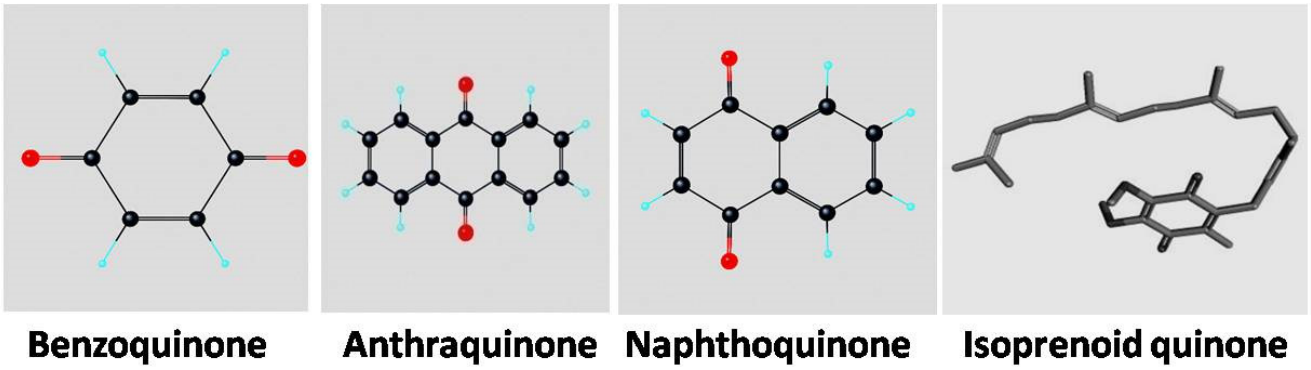

Fig. 1: Types of quinone classes

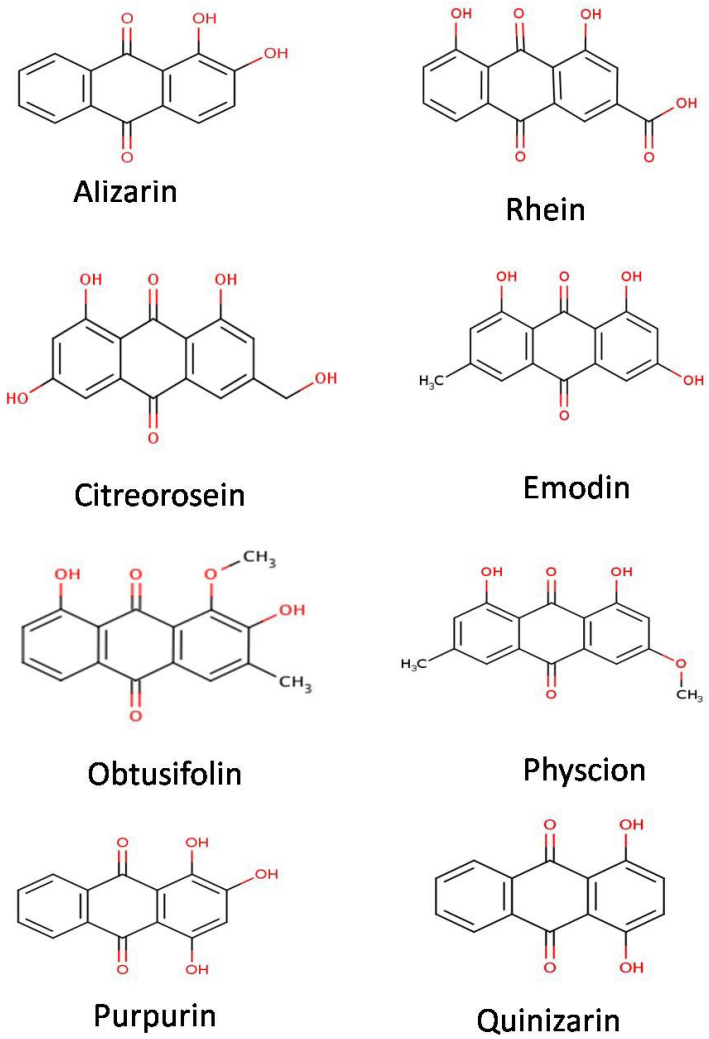

Fig. 2: Structures of different natural anthraquinones

TABLE 1: NATURAL SOURCE OF ANTHRAQUINONES (FAMILY & AVAILABILITY)

S No	Name of Plant species	Family	Availability	Compounds
1	*Cassia nigricans* Vahl.	Fabaceae	Indian	Emodin
2	*Cassia obtisufolia*	Fabaceae	Indian	Obtusifolin
3	*Cassia occidentalis* L. var. aristata Collad.	Fabaceae	Indian	Emodin
4	*Cassia tora* Linn.	Fabaceae	Indian	Obtusifolin, Emodin
5	*Dendrobium thyrsiflorum* Rchb. f. ex Andre	Orchidaceae	Indian	Emodin
6	*Lantana camara* Linn	Verbenaceae	Indian	Emodin
7	*Morinda citrifolia* L.	Rubiaceae	Indian	Alizarin
8	*Morinda tinctoria* Roxb.	Rubiaceae	Indian	Alizarin
9	*Polygonum cuspidatum* Sieb. et Zucc.	Polygonaceae	Exotic	Emodin
10	*Polygonum multiflorum* Thunb.	Polygonaceae	Exotic	Emodin
11	*Rhamnus cathartica* L.	Rhamnaceae	Exotic	Emodin
12	*Rheum officinale* L.	Polygonaceae	Exotic	Emodin
13	*Rheum palmatum* L.	Polygonaceae	Indian	Emodin
14	*Rubia cordifolia* Linn.	Rubiaceae	Indian	Alizarin, purpurin, quinizarin
15	*Rubia tinctorium* L.	Rubiaceae	Indian	Alizarin, purpurin, quinizarin
16	*Rumex chalepensis* Mill.	Polygonaceae	Exotic	Emodin
17	*Rumex obtusifolius* L.	Polygonaceae	Exotic	Emodin
18	*Ventilago leiocarpa* Benth	Rhamnaceae	Exotic	Emodin
19	*Ventilago madraspatana* Gaertner	Rhamnaceae	Exotic	Emodin

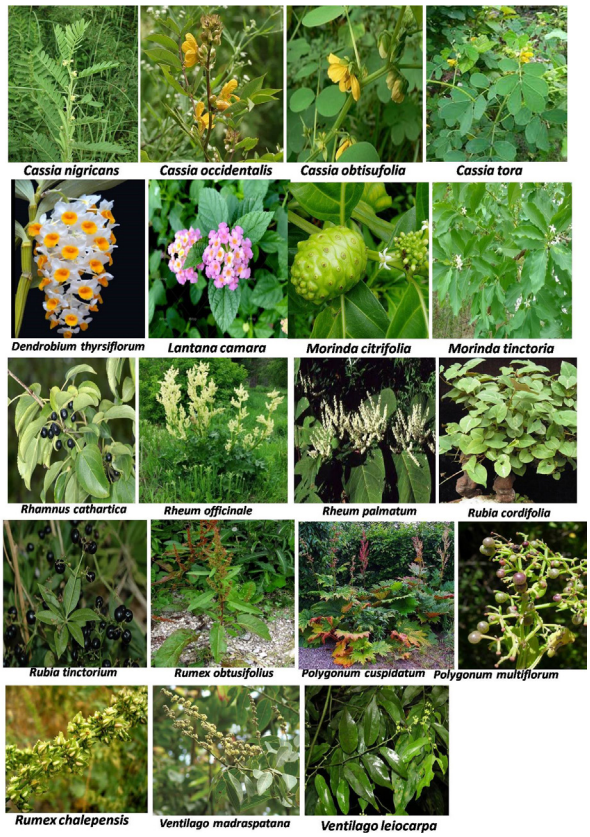

Fig. 3: Natural sources of different anthraquinones

ALIZARIN

Structural facts:

IUPAC Name: 1,2-dihydroxyanthracene-9,10-Dione; Group: Anthraquinone; Common name: Mordant Red 11, turkey red, rose madder; Molecular formula: $C_{14}H_8O_4$; Molecular weight: 240.214 g/mol; Texture: Orange red crystal; Boiling point: 430°; Melting point: 279-283°; Density: 1.540 g/cm3; Solubility: Soluble in organic solvents like DMSO.

Natural source:

It is one of the main constituents found in plants of the Rubiaceae family, especially in *Rubia tinctorium, Rubia cordifolia, Morinda tinctoria, Morinda citrifolia*[27,28].

Description:

Alizarin, due to its red colouration, is broadly utilised in textile industries[33]. It has three equilibrium structures depending on the pH of the solution[34]. Alizarin forms stable complexes with Al^{3+}, known as "lake pigments".

Ethno-pharmacological uses:

Antioxidant activity: Free radicals mostly generated during normal metabolism of living cell. These are quite unstable and hamper normal cell activities to balance themselves leading to severe health crisis. However, neutralization of their activities is the vital process involved in diseases prevention. The antioxidant activity of alizarin has been well established by several researchers[35-38].

Osteotropic activity: Alizarin is being used as a neo technique for bone cancer treatment due to its antitumor properties[39]. In low dosages, it strongly inhibited the osteosarcoma and breast carcinoma cell proliferation. Furthermore its selective inhibitory activity on normal and cancerous cells makes it more efficient[40].

Dye: It is used as a chromophore and a dye. It is principally used for dyeing fabrics in textiles due to presence of red pigmentation[33]. It also enables red-mineralization for expression of osteogenesis markers (Runx2 and osteocalcin), which elevated osteoblast differentiation.

Anti-inflammatory activity: The anthraquinone has an effective anti-inflammatory efficacy in suppressing macrophages and neutrophils relevant to inflammation[41,42].

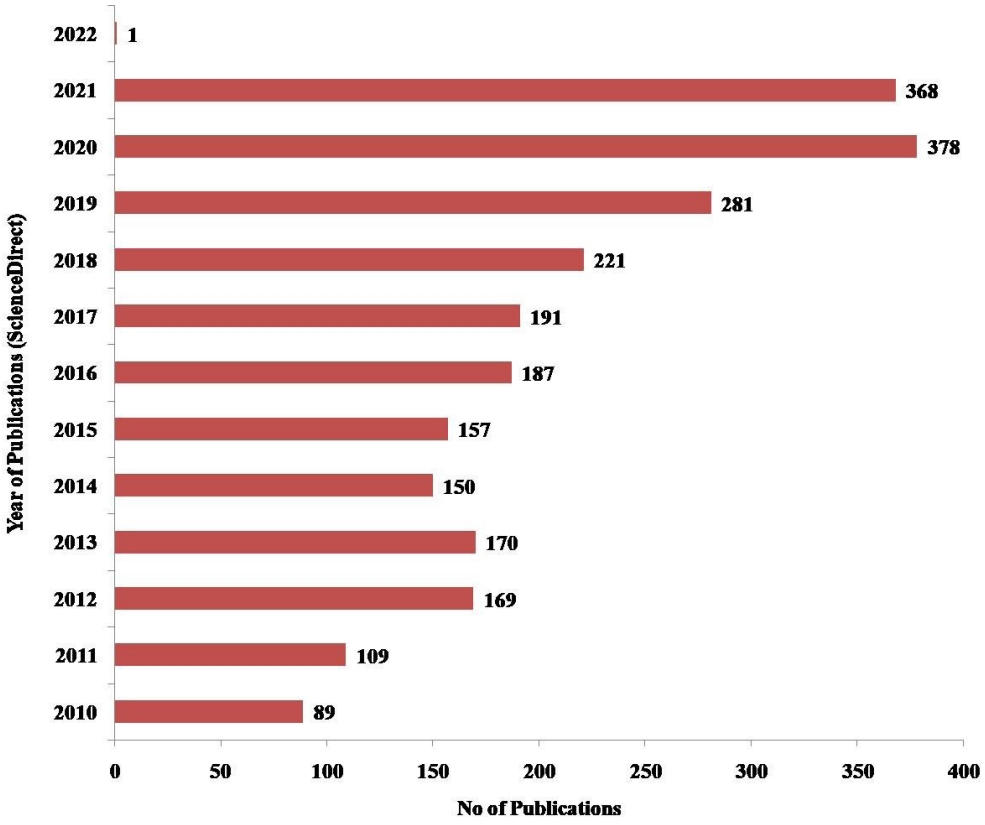

Fig. 4: Papers published under anthraquinone phytochemical uses

Chromogenic agent: Alizarin red S has been widely used for validation of antidepressant drug Dothiepin Hydrochloride (DOTH) in drug formulations by development of ion-pair complex between DOTH and alizarin red S[43]. It is also used for validation of anti-allergic drug, fexofenadine hydrochloride by development of ion-pair complex between fexofenadine hydrochloride and alizarin red S[44].

EMODIN

Structural facts:

IUPAC name: 1,3,8-trihydroxy-6-methylanthracene-9,10-Dione; Group: Anthraquinone; Common name: Emodol, frangula emodin; Molecular formula: $C_{15}H_{10}O_5$; Molecular weight: 270.24 g/mol; Texture: Orange powder; Boiling point: sublimes; Melting point: 257°; Density: 1.231 g/cm^3; Solubility: Insoluble in water; soluble in alcohol, alkali hydroxide, sodium carbonate and ammonia solution

Natural source:

Emodin is abundantly found in three families: Fabaceae (*Cassia tora, Cassia occidentalis* and *Cassia nigricans*), Polygonaceae (*Rheum palmatum*, *Rheum officinale*, *Rumex obtusifolius*, *Rumex chalepensis* and *Polygonum cuspidatum*, *Polygonum multiflorum*)[45] and Rhamnaceae (*Rhamnus cathartica* and *Ventilago leiocarpa*, *Ventilago madraspatana*)[46]. It is also available in Asteraceae, Poaceae and Simaroubaceae[47]. It has a worldwide distribution, occurring in subtropical and tropical families *Lantana camara*, *Dendrobium thyrsiflorum*; in families that mainly inhabit the temperate region[48] and in families present in both tropics and temperate regions (Rhamnaceae and Clusiaceae)[49].

Description:

Emodin structurally is substituted by hydroxyl and methyl groups at 1st, 3rd, 8th and 6th positions. It is a tyrosine kinase inhibitor, an anti-neoplastic agent and a laxative[50,51].

Ethno-pharmacological uses:

Anti-bacterial activity: Emodin has been reported to have antibacterial activities against *Arthrobacter globiformis*, *Chlorella pyrenoidosa*, *Bacillus megaterium*, *Rhizobium* spp., and *Azotobacter chroococcum* with minimal concentrations of 10-200 µg/ml[52-54]. It is also found to be potent against *Helicobacter pylori*[55].

Anti-Multidrug Resistance (MDR) activity: Due to wide spectrum utilization of antibiotics in each and every disease, their efficacy has been sacrificed in terms of both quantity and quality. This creates a serious concern as the targeted pathogens are kind of getting immunity or adapting to the biochemistry of the concerned antibiotics thereby producing MDR strains. The MDR activity of tumor cells is a crucial problem in treating cancer. In such situation, some bio-active compounds like emodin are potent enough to break this MDR action of cancer cells making them sensitive towards treatment by blocking certain pathways[56]. It also reduces glutathione level and down regulates MDR protein expression in cancer cells[46].

Anticancer activity: In particular, emodin exhibits cytotoxic effects through the arrest of cell cycle and induction of apoptosis in cancer cells[46]. Emodin-induced apoptosis in human cervical cancer Bu25TK cell occurs through poly (adenosine diphosphate ribose) polymerase cleavage and activation of caspase-9[57]. Moreover, it triggers apoptosis in HepG2/C3A, PLC/PRF/5 and SK-HEP-1 cells through a p53-dependent pathway[58]. In addition, emodin accelerates arsenic trioxide-induced apoptosis[59] and even gene expression alteration occurs in HeLa cells through the redox-dependent enhancement of arsenic cytotoxicity[60]. It has cytotoxic activities against multiple myeloma[61] and also induces apoptosis in human tongue squamous cancer SCC-4 cells through mitochondria-dependent pathways *in vitro*[62].

Anti-diabetic activity: Emodin isolated from rhizome of *Rheum palmatum* exhibit anti-diabetic properties through insulin-stimulated glucose transport mechanism[63].

OBTUSIFOLIN

Structural facts:

IUPAC Name: 2,8-dihydroxy-1-methoxy-3-methylanthracene-9,10-Dione; Group: Anthraquinone; Common name: Obtusifolin; Molecular formula: $C_{16}H_{12}O_5$; Molecular weight: 284.267 g/mol; Texture: Yellowish powder; Boiling point: 528° at 760 mm Hg; Melting point: 242-243°; Density: 1.448 g/cm3; Solubility: It is soluble in chloroform, dichloromethane, ethyl acetate, DMSO.

Natural source:

It is ubiquitously found in plants from Caesalpinaceae

family *viz. Cassia obtisufolia*, *Cassia tora*[64,65].

Description:

Obtusifolin is group of dihydroxy anthraquinone with several pharmaceutical medicament applications including antioxidant and antidiabetic activity[66].

Ethno-pharmacological uses:

Anti-obesity activity: Obtusifolin from *Cassia tora* was found to possess anti-obesity activity that regulates the lipid metabolism and used to treat obesity[66,67].

Pharmacokinetics study: The validation study of obtusifolin for pharmacokinetic activity through liquid chromatography with tandem mass spectrometry analysis in rats were detected through negative ion electrospray ionization with AUC_{0-t} and $AUC_{0-\infty}$ values were 491.8±256.7 and 501.7±256.7 ng×h/ml and elimination half-life of 3.1±0.7 h. This provided pharmacological insight to obtusifolin[68].

Antibacterial activity: Ethanolic and aqueous extracts of leaves of *Cassia tora* were evaluated for antibacterial activity against selected pathogenic microbes. Both the extracts showed higher antimicrobial efficacy with minimum inhibitory concentration[69].

Antifungal activity: Crude extracts of leaves of *Cassia tora* were investigated for antifungal activities against dermatophytes basically trichophyton and epidermophyton, through well diffusion method[70].

Treatment of Alzheimer's disease: A variety of traditionally used plants extracts were evaluated for modulation of Aβ-producing secretase activities and Aβ-degradation mechanism. In this study obtusifolin, was found to inhibit acetylcholinesterase activity *in vitro* and *ex vivo* along with possessing remarkable antioxidant and heavy metal chelating activities[71,72]. Obtusifolin, obtained from Cassia obtusifolia, lowers cellular reactive oxygen species and malondialdehyde production by enhancing antioxidant activities with mitochondrial complex I/III. It also enables X chromosome linked inhibitor of apoptosis up regulation along with cysteinyl aspartate specific proteinase 3/9 and poly adenosine diphosphate ribose polymerase down regulation, thereby protecting mitochondrial against apoptosis by inhibiting Omi/HtrA2 release[73].

Anti-inflammatory activity: The anti-inflammatory activities of obtusifolin from *Senna obtusifolia* (L.) H.S.Irwin and Barneby was studied. The intake of Obtusifolin was found to inhibit metalloproteinase 3, metalloproteinase 13 and cyclooxygenase 2 along with lowering collagenase activity and the PGE2 level. It reduces the cartilage damage by regulation of metalloproteinases and cyclooxygenase 2 expressions[72].

PURPURIN

Structural facts:

IUPAC Name: 1,2,4-trihydroxyanthracene-9,10-Dione; Group: Anthraquinone; Common name: Verantin, smoke brown G, hydroxylizaric acid; Molecular formula: $C_{14}H_8O_5$; Molecular weight: 256.213 g/mol; Texture: Brown to brown-red powder; Boiling point: 359.45°; Melting point: 253-256°; Density: 1.659 g/cm3; Solubility: Soluble in water (partly), alcohol, ether DMSO (~0.5 mg/ml)

Natural Source:

It is found in the plant *Rubia cordifolia*, *Rubia tinctorium* (Rubiaceae)[74].

Description:

It is a trihydroxy anthraquinonederrived from anthracene by substitution with oxo groups at C-9 and C-10 and with hydroxyl groups at C-1 and C-4.

Ethno-pharmacological uses:

Antioxidant activity: Antioxidant effect of purpurin was studied by several researchers using various *in vitro* and *in vivo* assays. Its antioxidant activity was studied against butrylcholinesterase, tyrosinase, acetylcholinesterase a-amylase and a-glucosidase. Purpurin found to have antioxidant and enzyme inhibition activity[37]. In another study antioxidant activity and phenolic compounds of traditional Chinese medicinal plants associated with anticancer, comprising 112 species from 50 plant families including *Rubia cordifolia* (purpurin) were measured showing higher values[75]. Purpurin treatment directly lowers antioxidative stress, thereby controlling down regulation system of NLRP3 leading to inhibition of inflammasome assembly scaffold[76].

Dye: Many of the plants used for dye extraction are classified as medicinal due to possession of vast array of secondary metabolites. Purpurin is actively used as a natural dye in fibre and textile industries, extracted from *Rubia cordifolia* and *Rubia tinctorum*[77,78].

Anti-fungal activity: The susceptibility of biofilm production by *C. albicans* against purpurin was studied in which results suggested the sub-lethal amount of Purpurin (3 µg/ml) can stop yeast-hypha transition. It also inhibited biofilm formation and reduced the metabolic activity of mature biofilms[79].

Pharmacokinetics study: The pharmacokinetic study on purpurin through Ultra Performance Liquid Chromatography Tandem Mass Spectrometery (UHPLC-MS/MS) method on rodent model found to has highest plasma concentration with 70.10±11.78 ng/ml C_{max} values with 0.82 g/kg of oral administration and maximal concentration at 1.61±0.24 h thereby giving slower absorption and metabolism[80].

Anti-inflammatory activity: Purpurin along with other natural had showed promising anti-inflammatory activity[41]. It also showed the anti-inflammatory activities by regulating the pro-inflammatory Interleukins (IL)-1β and IL-18 systems[76].

Neuro-protective activity: Long duration treatment with purpurin validated serotonin linked activity on p-chloro phenylalanine-induced depression by suppressing Monoamine Oxidase (MAO) associated brain metabolism[81]. Even molecular docking simulation validated major purpurin and MAO-A binding affinity than that of purpurin and MAO-B[82]. Purpurin also crosses blood–brain barrier thereby regulating neurological disorders[83].

QUINIZARIN

Structural facts:

IUPAC name: 1,4-dihydroxyanthracene-9,10-Dione; Group: Anthraquinone; Common name: 1,4-dihydroxyanthraquinone; Molecular formula: $C_{14}H_8O_4$; Molecular weight: 240.214 g/mol; Texture: Orange reddish crystalline powder; Boiling point: 450°; Melting point: 200°; Density: 1.3 g/cm^3; Solubility: Moderately soluble in alcohol, soluble in ether and benzene.

Natural source:

It is found in plants of Rubiaceae family (*Rubia tinctorium, Rubia cordifolia*)[79].

Description:

Quinizarin has hydroxyl substituent at 1st and 4th positions through alternation of H atom from hydroxyl group hence called as dihydroxyanthraquinone.

Ethno-pharmacological uses:

Anti-inflammatory activity: The anti-inflammatory activity of quinizarin along with other natural quinones was evaluated[41].

Antioxidant activity: The antioxidative activity of quinizarin was measured through various enzymatic assays. The enzyme inhibitory activities were also analyzed against acetylcholinesterase, butrylcholinesterase, tyrosinase, a-amylase and a-glucosidase. It was found to have antioxidant and enzyme inhibition activity[37].

Anti-proliferative and anti-metastatic activity: Quinizarin anticancer activity was done against B16-F10 melanoma murine cells[84], in which the tumor cell growth was inhibited after treatment with danthron and quinizarin. The overall result suggested that both the compounds possess significant antineoplastic activity[85].

Anti-cancer activities: Photosensitive compounds like emodin and quinizarin have shown antineoplastic activity and antitumor activities and are utilized for photodynamic therapy for cancer[86]. The molecular docking and dynamics simulation research had verified its binding affinity and structural stability towards anti-apoptotic Bcl-2 protein[87].

CONCLUSION

Aanthraquinones are one of unique quinones with broad spectrum pharmaco-therapeutic utilization in several drug formulations. The versatility of these compounds is mostly due to their structural pattern along with the plants in which they are being synthesized. The 6 unique anthraquinone compounds depicted in the review article helps in depicting their natural resources, structural pattern and pharmacological potency. The gathered information would be helpful in precise identification of these compounds from a wide range of natural resources for further pharmao-clinical studies for drug formulation applications thereby lessening the threat status of the frequently used rare, endangered and threatened plants.

Conflict of Interest:

The authors report no conflicts of interest.

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