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EXPLORATION OF THERAPEUTIC POTENTIAL OF ANTHRAQUINONES AND FLAVONOIDS ISOLATED FROM DIFFERENT SPECIES OF *Cassia:* A PROMISING JOURNEY FROM ETHNOMEDICINE TO BIOMEDICINE

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ABSTRACT

The present communication is a brief compilation of promising therapeutic efficacies of several anthraquinones and flavonoids isolated and characterized from some selected species of *Cassia*, a common uncared medicinal plant belonging to the family Caesalpiniaceae. Most of the species of this particular genus are well reputed in Indian system of medicine for treatment of various ailments among which cure against dermatological diseases and liver complaints, activities as laxatives, antimutagenic, antioxidant, immunomodulatory, antidiabetic, estrogenic, antimicrobial, anthelmintic and hypolipidemic activities are worth-mentioning. The plant not only serves as a good commercial source of natural anthraquinones but also has stepped into formulation of several herbal remedies like Liv. 52, Herbolax, Bonnisan, Pilex, Diasulin etc. The different pharmacological and therapeutic activities as revealed from various research activities using modern scientific approaches proclaim its possibility to enter into biomedical formulations in near future. In view of this, an attempt has been made to provide a vivid scenario of how the traditional uses of this plant in the name of ethnomedicine has been tuned to produce effective herbal formulations and is gradually approaching towards isolation of effective drug for formulation of marketed therapeutics.

KEYWORDS: Anthraquinone, *Cassia,* Pharmacology, Traditional Use, Therapeutic.

Although continuous search for potent bioactive phytochemical compounds through screening of innumerable medicinal plants has been a common practice worldwide, however the study of weeds as potential source of useful drugs has gained little importance so far in the world of medicine. The members of Leguminosae are considered as a vast group of plants of immense importance to mankind. From food to fibre, from atmospheric nitrogen fixers to timber producers, from medicines to dyes they have covered almost all areas of utilitarian aspects. The genus *Cassia* is one of the major representatives of leguminous groups comprising of about 600 species (Dave and Ledwani, 2012) belonging to the sub-family Caesalpinioideae and many species under the genus although possess promising medicinal attributes are usually less attended due to their identity as gregarious weeds. The commonly occurring species taken up for our study are *Cassia tora, C. occidentalis, C. alata* and *C. auriculata* which are mostly found along the roadsides, wastelands, agricultural fields etc. Due to random cutting and felling of these plants from their natural habitats as obnoxious weeds, documentation of such medicinally important weeds has become the need of the hour. All these species are well recognized in traditional system of medicine for their therapeutic activities like purgative, analgesic, antimicrobial, anti-tumourogenic, antimutagenic, hepatoprotective, hypoglycaemic, immunomodulatory, antidiabetic, anti-inflammatory, various skin ailments like ringworm, psoriasis, dermatitis and eczema (Dave and Ledwani, 2012; Singh et al. 2013; Deshpande and Bhalsi, 2013). The genus *Cassia* is remarkably considered as a rich repository of natural anthraquinones, flavonoids and phenolic compounds (Dave and Ledwani, 2012; Singh et al. 2013; Choudhary et al. 2011) and the compounds emodin, chrysophenol and rhein being widely distributed throughout the *genus* are considered as chemotaxonomic markers for this genus (Ganapaty et al. 2002). Anthraquinones are a group of functionally diverse aromatic chemicals with parent structure 9,10-dioxoanthracene. They are used as laxatives mainly from their glycosidic derivatives, the most effective ones being O-glycosides of dianthrones and anthraquinones as well as C-glycosides of anthrones. These derivatives show antioxidant properties and have been valued for their cathartic and detoxifying action (Dave and Ledwani, 2012). Since many of these compounds have been isolated and characterized from different species of *Cassia* and their effects have been assessed both *in vitro* and *in vivo* experimentations for establishment of various pharmacological implications, the present communication mainly highlights all those scientific efforts which escalate the importance of ethnobotanically originated crude drug towards the discovery of pharmaceutical

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products or more appropriately biomedicines. The review comprises of a brief introduction of the traditional knowledge of the selected species of *Cassia* as ethnomedicine (Table 1), tabulates the pharmacological activities of anthraquinones, flavonoids as well as their derivatives so far isolated from them (Table 2) and finally discusses about the polyherbal formulations which are available in the market from different species of *Cassia* (Table 3). In addition to Mercina capsule and Hyponidd tablet, some other polyherbal marketed formulations of *Cassia auriculata* like Dianex, Diamed, Aavirai kudineer and Madhumeha churna have also proved their efficacy *in vivo* as antihyperglycaemic and antidiabetic agents. (Kainsa et al. 2012). Thus the future prospect of the isolated phytochemicals are thoroughly discussed which are potent enough to be developed into biomedicines after proper clinical trial.

Table 1: Ethnomedicinal importance of some selected species of *Cassia.*

Name of the species	Ethnomedicinal uses
1.*Cassia occidentalis*	**Whole plant:** Plant extract is used in curing eye inflammation in Ayurveda. Also used in Jamaican folk-medicine for curing diarrhea, dysentery, constipation, fever, cancer, eczema and venereal diseases (Dave and Ledwani, 2012). It is also used to cure sore of eyes, hematuria, rheumatism, typhoid, asthma, disorder of haemoglobin, leprosy. An infusion of bark is given in diabetes (Khare 2004). **Root:** A paste made out of roots is considered as a specific remedy for ringworm, eczema and other skin ailments (Kathirval and Sujatha, 2011-2012)**.** Infusion of roots (10-20g) considered useful in obstruction of stomach and incipient dropsy. Roots are also used as veterinary medicines for animal diseases and as antidote in case of poison. It is also used against gastric complaints, to increase lactation, in whooping cough etc. Decoction of roots with black pepper is used for filarial disease (Dave and Ledwani, 2012) **. Leaves :** Leaf paste applied on healing wounds, sores, itch and cutaneous diseases. It is also used in bone fracture, fever, ringworm, skin diseases, throat infection and wounds. Twigs are used as tooth brushes, leaves are burnt and the soot obtained is mixed with coconut oil and applied on eye-lids for cooling sleep (Dave and Ledwani, 2012)**. Seeds:** Seeds are brewed into a coffee like beverage for asthma, malaria, fevers and stomach complaints. It acts as a purgative too (Khare 2004). **Pods:** The 8-10 roasted seeds of this plant are eaten for cough problems in India. Decoction of fruits are used in the treatment of mental disorders (Dave and Ledwani, 2012)**.**
2. *Cassia tora*	**Whole plant:** 2 Ayurvedic preparations—'Dadrughan-vati' and 'Chakramardha tailamu' are beneficial for ringworm, eczema, leucoderma and other skin diseases.The plant also pacifies dandruff, constipation, cough, hepatitis, fever and haemorrhoids. **Root:** Root is used as bitter tonic, stomachic, antidote against snake bite, in worm infection, abdominal tumours, bronchitis, asthma. **Leaves:** Used as antiperiodic, in liver disorders, paste of leaves applied to ringworm, eczema,cut wounds, ulcers. Decoction of leaves used as laxative, in gout, sciatica and joint pain. **Seeds:** Used in eye diseases, liver complaints, ear aches, leprosy, psoriasis, in vision improvement, diuretic, lowering cholesterol and blood pressure (Choudhary et al., 2011) **.**
3. *Cassia alata*	**Whole plant:** Bark used to treat skin diseases. Extract of aerial parts is CNS depressant, diuretic and anti-inflammatory. Used to treat bronchitis and asthma. **Leaves:** Antiparasitic, used in eczema, bronchitis, asthma, ringworm and snake bites. Herbal lotion prepared from leaves is used in tinea infections, scabies, herpes, blotch, eczema, mycosis, purgative. Decoction of leaves and flowers used as expectorant. **Root:** In Surinam, root extract used to treat uterus disorder (Meenupriya et al. 2014).
4. *Cassia auriculata*	**Whole plant:** Treatment of skin diseases, asthma, conjunctivitis and renal disorders. Used as a cure for rheumatism and diabetes. **Leaves:** Used in chronic fever, skin diseases, stomachic, treatment of diabetes, thermogenic, constipating and expectorant. **Seeds:** Bitter, astringent, cooling, ophthalmic, diuretic (Dave and Ledwani, 2012)**.** **Flowers:** dried powder with goats milk taken orally to prevent white discharge in women, used in diabetes, dandruff. **Roots:** Useful in urinary discharges, cures tumours, skin diseases and asthma. Powder of bark used for chronic dysentery (Kainsa et al. 2012).

Table 2: Pharmacological activities of isolated anthraquinones and flavonoids from selected species *Cassia.*

Name of the species	Active constituent (s)	Type of extract	Type of Activity	References
1.***Cassia occidentalis***	i) Emodin	Ethanolic root extract	Antibacterial activity	Chukwujekwu, 2006.
	ii)1,8 dihydroxy anthra- quinone, emodin	Ethanolic and chloroform extract of root bark	Antimalarial activity	Winter et al., 1995; Batista et al., 2009; Pandeti et al., 2014
	iii) Chrysophanol	Isolated from fraction of methanolic extract of leaves	Hepatoprotective activity (in vivo)	Rani et al., 2010.
	iv) 4,4′5,5′-Tetrahydroxy-2,2′-methoxy-9,9′-bisanthraquinone	Isolated from methanolic fraction of aqueous extract of seed	Hepatoprotective activity	Sastri et al., 2011.
	v) Chrysophanol, aloe-emodin, emodin, rhein vi) Chrysophanone, emodin	Isolated from root and seed extract Isolated from seed extract	Laxative/purgative activity Wound healing property	Vijayalakshmi et al., 2013. Abu-Darwish & Ateyyat, 2008
2. *C. tora*	i) Chrysophanol and Obtusifolin	Ethyl acetate extract of seeds	*In vitro* inhibitory activity on protein glycation	Jang et al. 2007.
	ii) Aurantio-obtusin, chryso-obtusin-2-O-beta-D-glucoside	Ethyl acetate extract of seeds	*In vitro* inhibitory activity on aldose reductase	Jang et al. 2007.
	iii) Chrysophanol, Emodin and Rhein.	Ethanolic/aqueous extract of leaves	Antigenotoxic properties	Das et al. 2011.
	iv)Flavonoids: Luteolin-7-*O*-β-glucopyranoside, quercitin-3- *O*-β-D-glucuronide,formononetin-7-*O*-β-D-glucoside	Seed extract	Anti-psoriatic activity	Vijayalakshmi and Geetha; 2014.
	v)Aloe-emodin, emodin, chrysophanol, rhein	Butanol fraction of methanolic extract	Immunostimulatory	Cherng et al.2008.
	vi)Naphthopyrone glucoside	Seed extract	Antidiabetic activity	Chaurasia et al. 2011; Lee et al. 2006.
	vii)Chrysophanol, chryso-obtusin and aurantio-obtusin	Methylene fraction of methanolic extract of seeds.	Antimutagenic	Das et al. 2011.
	viii)Cassiaside, rubro-fusarin gentiobioside, alaternin	Butanol fraction of methanolic extract of seeds	Antimutagenic	Das et al. 2011.
	ix)Aurantio-obtusin	70% ethanolic extract of seeds	Estrogenic activity, antiallergic activity	Das et al. 2011; Ki et al. 2015.
	x)Aloe- emodin, 1,8-dihydroxy-3-(hydroxymethyl)-anthraquinone	Methanolic extract of leaf	Purgative activity	Maity and Dinda ; 2003
	xi) Emodin, aloe-emodin	Methanolic extract of seed	Purgative activity	Maity and Dinda ; 2003
	xii) Ononitol monohydrate	Ethanolic extract of leaves	Hepatoprotective agent (in vivo)	Das et al. 2011.
	xiii) Cassiaside, rubrofusarin,	Seed extract	Hepatoprotective agent	Das et al. 2011.

	rubrofusarin-6-β-gentiobioside			
	xiv) Emodin, physcion, rhein, aloe-emodin	Chloroform fraction of ethanolic extract of seed and leaves	Antifungal activity (in vivo)	Choudhary et al., 2011
	xv) Chrysophanic acid-9-anthrone, chrysophanol	Aqueous extract of defatted seed	Antifungal activity	Das et al. 2011.
	xvi) Torachrysone, toralactone, aloe-emodin, rhein, emodin	Aqueous extract of seed	Antibacterial activity	Choudhary et al., 2011
	xvii) Alaternin, cassiaside, rubrofusarin gentiobioside	Seed extract;	Antioxidant activity	Das et al. 2011.
	xviii) Glucoaurantioobtusin	Methanolic extract of seed	Hypotensive activity	Choudhary et al., 2011
	xix) Emodin	Leaf, stem and seed extract	Antioxidant activity, Antitumour activity,	Meena et al.2010; Jain and Patil 2010.
3. *C.alata*	i) Rhein and Kaempferol	Hydro-methanolic extract of leaves	Antiallergic activity	Singh et al. 2012.
	ii) Kaempferol-3-o-sophoroside	Leaf extract	Analgesic & anti-inflammatory	Palanichamy and Nagarajan; 1990. Palanichamy and Nagarajan; 1990.
	iii) Kaempferol-3-o-gentiobioside	Leaf extract	Anti-inflammatory activity	Meenupriya et al. 2014
	iv) Kaempferol & Kaempferol-3-o-gentiobioside	Ethyl acetate and n-butanol fraction of methanolic extract of leaves	Antidiabetic activity	Varghese et al. 2013.
	v) Chrysophanic acid, chrysophanol, rhein, aloe-emodin,emodol, 4,5-dihydroxy-2-hydroxymethylanthraquinone, 4,5-dihydroxy-1-hydroxy methyl anthrone	Aqueous and ethanolic extract of leaves	Antifungal activity	Phongpaichit et al. 2004.
	vi) 1,3,8 trihydroxy -6-methyl anthraquinone, Kaempferol-O-diglucoside, quercitin-O-glucoside, Kaempferol, rhein, danthrone	Ethanolic & Methanolic extract of leaves	Antibacterial	Meenupriya et al. 2014
4. *C. auriculata*	i)DL-α-tocopheryl-α-D-mannopyranoside, DL-α-tocopheryl-β-D-galactopyranoside	Methanolic extract of leaves	Antiallergic and anti-inflammatory activities	Meenupriya et al. 2014
	ii)5-O-methylquercitin-7-O-glucoside	Methanolic extract of flower	Anti-inflammatory activity	Meenupriya et al. 2014
	iii) Quercetin (a flavonol) iv)1,3,8 trihydroxy-6-methyl-anthraquinone	Methanolic extract of flower Methanolic extract of leaves	Antioxidant activity Activity against oral microflora	Meenupriya et al. 2014 Meenupriya et al. 2014

Table 3: Species of *Cassia* used in marketed polyherbal formulations.

Polyherbal remedy	Name of the plant (s)	Therapeutic use
1. **Liv. 52** tablets and syrup [Himalaya Health Care]. (*about 24 clinical reports; 92 experimental papers)	***C. occidentalis****, Capparis spinosa, Cichorium intybus, Solanum nigrum, Terminalia arjuna, Achillea millefolium, Tamarix gallica*	Hepatoprotective, management of Hepatitis A.
2. **Herbolax capsule** [Himalaya Health Care]. (*about 3 clinical papers)	***C. occidentalis*** (main ingredient)	Anti-constipation.
3. **Bonnisan drops** [Himalaya Health Care]. (*about 08 clinical papers)	***C. occidentalis****, Tinospora cordifolia, Piper longum, Capparis spinosa, Emblica officinalis, Cichorium intybus, Terminalia chebula, Achillea millefolium, Tamarix gallica,Tribulus terrestris, Boerhaavia diffusa, Elettaria cardamomum* and Dill oil.	Gastrointestinal discomfort in infants (Dave and Ledwani, 2012).
4.**Purim tablet** (Himalaya Drug Co.) [Dose: 1-2 tablets twice daily]. (*6 clinical papers)	***C. fistula****, Curcuma longa, Psoralea corylifolia, Saussurea lappa, Picorrhiza kurroa, Azadirachta indica, Tinospora cordifolia, Crataeva magna,* Triphala*, Embelica ribes, Andrographis paniculata*	Effective against acute and chronic dermatitis, eczema, acne, anthelmintic, improves liver function, act as natural detoxifier.
5. **Pilex tablet & ointment** (Himalaya Drug Co.) [Dose: 1/2tablets twice or thrice daily]. (*18 clinical papers)	***C. fistula****. Commiphora wightii*, purified Shilajit, *Azadirachta indica*, Triphala, *Berberis aristata, Bauhinia variegate, Mesua ferrea*	Helpful in bleeding or non-bleeding piles, haemorrhoids, varicose veins, anal discomfort.
6. **Orthoease capsules** (Universal Pharmaceuticals Ltd.) [2 capsules twice daily]	***C. fistula****, Commiphora mukul,*Yogaraja guggulu choornam, *Alpinia galangal, Acorus calamus, Withania somnifera* etc.	Herbal supplement for joint care and arthritis.
7. **Hadensa capsules (ayurvedic) & ointment (allopathic) (**Dollar Company Pvt. Ltd). [1 capsule 3 times daily after meal].	***C. fistula****, Plumbago zeylanica*, Triphala, *Zingiber officinalis,Curcuma aromatic, Vitex negundo, Azadirachta indica, Withania somnifera, Piper nigrum, P. longum, Abies webbiana* etc	Capsules used for piles, also has laxative and wormicidal property. Ointment used in piles, anal fistula and fissures.
8. **Xpiles tablet** (Surya Herbal)	***C. fistula****,* pure guggul, *Azadirachta indica, Mimosa pudica, Aegle marmelos, Triphala, Bhasma Shilajit, Berberis aristata, Bauhinia variegate, Mesua ferrea*	Piles, constipation.
10. **Mercina capsules** (J & J Dechan brand). [1-2 capsules ½ an hr. before breakfast, lunch & dinner].	***C. auriculata****, Gymnema sylvestre, Momordica charantia, Syzygium cumini, Phyllanthes emblica, Melia azadirachta, Trigonella foenum-graecum, Coccinia indica, Tinospora cordifolia*	Anti-diabetic- Effective control of maturity onset non-insulin dependent diabetes mellitus.
11. **Hyponidd tablet** (Charak Pharma Pvt. Ltd) [2 tablets twice daily for 3-6 months]	***C. auriculata****, Gymnema sylvestre, Momordica charantia, Melia azadirachta, Eugenia jambolana, Pterocarpus marsupium, Tinospora cordifolia, Enicostemma littorale, Embelica officinalis and Curcuma longa.*	Insulin sensitizing drug to cure early diabetes in women with polycystic ovarian syndrome.
12. **Diasulin**	***C. auriculata,*** *Coccinea indica, Curcuma longa, Momordica charantia,Scoparia dulcis, Gymnema sylvestre, Embelica officinalis, Syzygium cumini, Tinospora cordifolia, Trigonella foenum-graecum,*	Antihyperlipidemic and antiperoxidative effect (Saravan and Pari, 2005).

*Source: himalayacentroamericana.com/himalaya_ research papers

CONCLUSION

From Table 2 it is revealed that compounds like chrysophanic acid-9-anthrone, alaternin, chryso-obtusin, aurantio-obtusin, rubrofusarin, cassiaside etc along with 1,8-dihydroxyanthrone derivatives like emodin, aloe-emodin, rhein, chrysophanol, physcion act as active principles for several pharmacological activities and their effect was found to be synergistic as well as specific. Thus it is expected that these species of *Cassia* together can assist in development of different herbal remedies after proper clinical trial. It may be also inferred that compounds like chrysophanol, chrysophanic acid-9-anthrone, rhein, aloe-emodin and physcion can act synergistically as potent antifungal agent especially against dermatophytes and hence promising enough for formulation of antifungal ointment. The isolated compounds like chrysophanol and ononitol monohydrate specifically have proved their potent hepatoprotective activities *in vivo* experimentally and await their clinical evaluation as hepatoprotective drug. The pharmacological effects as revealed from different studies indicate the efficacy of this plant as a potent purgative, antiallergic, anti-inflammatory, anti-diabetic and hepatoprotective agent. The present review thus provides a useful database of the immense therapeutic contributions of *Cassia* made by the isolated anthraquinones, their derivatives and flavonoids in the field of ethnopharmacology and throw light towards the ongoing development and marketing of modern herbal drugs. Thus in order to obtain lead compounds for further new drug discovery, isolation, standardization and clinical evaluation of such phytochemicals is the need of the hour through significant advances in study design and sophisticated instrumentation which will actually complete the journey from the indigenous knowledge of traditional medicine to formulation of biomedicinal products.

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