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Review Article

Secondary Metabolites of the Genus *Crotalaria* (Rattlepods) and their Medicinal Importance – A Review

Muhammad Sarwar Yaqub[a], Bushra Basher[b] and Rozina Aslam[b]*

[a] Department of Horticultural Sciences, The Islamia University of Bahawalpur, Pakistan
[b] Department of Chemistry, The Islamia University of Bahawalpur, Pakistan

ABSTRACT

This review describes the genus *Crotalaria* focusing on its secondary metabolites and their medicinal applications. The genus *Crotalaria* of Fabaceae or Leguminosae family have about 600 species which are distributed in tropic and sub-tropic regions of the world. They are medicinally important due to production of various compounds. Traditional early medicines and drug discovery were based on natural products. Organisms produce some chemical compounds by their metabolic pathways that are not necessary for their growth and development and are known as secondary metabolites. This diverse group of compounds is synthesized by algae, plants, animals and fungi. These metabolites consist of variety of compounds such as phenols, coumarins, terpenoids, flavonoids, alkaloids, steroids and fatty acids. Secondary metabolites obtained from *crotalaria* exhibit anticancer, anti-rheumatoid arthritis, anti-allergic, antioxidant, antimicrobial, antiaging and wound healing activities along with many other medicinal applications.

Keywords: *Alkaloids, coumarins, Fabaceae, natural products, steroids, terpenoids.*

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INTRODUCTION

Living organisms produce chemical compounds or substances called natural products (Anulika et al., 2016). From ancient time the plant metabolites and human being have relationship. Natural sources like microorganisms and plants have ability to produce biologically active compounds against different diseases (Jabeen et al., 2014). Traditionally early medicines and drug discovery were based on natural products (Butler, 2005). These potential natural product derived substances have advantages and disadvantages (Debbab et al., 2010). They have been used for treatment and cure of diseases from the beginning of civilization (Scarim et al., 2017). Today many drugs are obtained from natural products derived from plants. From approximately the early 1980s, drug discovery from natural products decreased because of the advent of combination chemistry technology that led to the future source of immense numbers of novel potential and new chemical entities (NCEs)/drugs (Newman, 2008). Due to new registration requirements, pesticides compounds are now being replaced by natural product-based pesticides (Dayan et al., 2009). However, pharmaceutical companies have not paid due attention to these compounds (Watkins et al., 2015).

FAMILY FABACEAE

The Fabaceae or Leguminosae, commonly known as the legume, pea, or bean family, is a large and economically important family of flowering plants (Rahman and Parvin, 2015). The family includes a large number of plants, comprising about more than 600 genera with about 18,000 species (Sharma and Kumar, 2013; Melo et al., 2010; Judd et al., 2002). Fabaceae is the most diverse plant family in the world with a wide distribution; considered as the third largest family of angiosperms in species numbers after Asteraceae and Orchidaceae in the global context (Beech et al., 2017; LPWG, 2017). The family has economic importance by having food crops that provide highly nutritious sources of protein and micronutrients which can benefit health and livelihoods, particularly in the developing countries (Gomes et al., 2018).

Economic importance of family Fabaceae

The plants of this family are source of protein because their roots contain nitrogen fixing bacteria. The plants are used as food such as pulses, gram and soya bean. Some of the plants are used as source of oil such as groundnut and soya bean. Sesbania and pea plants are used as ornamental plants. Shishum and Sunn hemp are used as timber and fiber, respectively. Indigo plant gives indigo dye (Meriem et al., 2014).

Medicinal importance of family Fabaceae

There is round about 150 plants of Fabaceae family which are commonly used by medicinal herbalists. For example, *Glycyrrhiza glabra* is an anti-inflammatory, antiviral, antioxidant herb and also used for disorder of liver and bronchi. The wild

* Corresponding author
E-mail: hlb92@yahoo.com (R. Aslam)

pea is used for the treatment of skin problems like acne and wrinkles; they have terpenes and flavonoids which have anticancer and antimicrobial activities, respectively. White and red *Cloves* are member of Fabaceae family which are used to cure skin problems like burn, rash, sore and ulcer. Alfalfa plant of this family contains vitamins A, B, E and K. Powdered roots of *Crotalaria albida* are used to cure victims of snake bite, while *Crotalaria pallida* is used to kill intestinal worms (Parvaiz et al., 2014).

GENUS *CROTALARIA*

Crotalaria is known as rattlepod. The common name rattlepod or rattlebox is taken from the reality that the seeds become loose in the pod as they mature, and rattle when the pod is shaken. The genus *Crotalaria* is considered as one of the largest genera having 600 species which are distributed in tropic and sub-tropic regions of the world (Devendra et al., 2012). *Crotalaria* species are mostly herbs and shrubs with simple unifoliate or digitally foliate leaves and stamens. Anthers are dimorphic. Flowers are yellow in color (Raj et al., 2011). The plants belonging to genus *Crotalaria* are commonly used as green manure (Daimon, 2006). The plants are also used for ornamental purposes. Its various plants are medicinally important such as seeds of *Crotalaria retusa* are used as medication for fever (Umerie et al., 2010). *Crotalaria juncea* has anti-obesity, antitumor and anti-diarrhea properties (Lalitha et al., 2011).

Crotalaria burhia is a fibrous plant and under shrub. In Pakistan it is commonly found in Punjab, Sindh, Khyber Pakhtunkhwa and Baluchistan. In India it is found in Punjab, Rajasthan and Gujarat. In different languages it has different names such as 'Shinio" in Rajasthan, 'Bhata' in Punjab, 'Ghughato' in Gujarat, 'Ghagri' in Marathi and 'Ban Sutri' in Bengal. Its Hindi name is 'Khip' (Katrria et al., 2012). Its leaves are elliptic-oblong or lanceolate. Flowers are yellow and in terminal racemes inflorescence. Seeds are sub-reniform, dark brown, compressed, shiny and smooth. Flowers and fruits are found throughout the year.

SECONDARY METABOLITES

Organisms produce chemical compounds by their metabolic pathways that are not necessary for growth and development of these organisms, called as secondary metabolites (Daniel et al., 2012). These products are intermediates of metabolism (Tiwari and Rana, 2015). Due to broad and no distinct boundaries they

Table 1: Compounds isolated from genus *Crotalaria.*

Sr. No.	Name of compound	Mol. formula & weight	Melting point (°C)	Source	References
1	Anacrotine	$C_{18}H_{25}NO_6$ (*m/z* 351.3991)	191-192	*C. trifoliastrum*	Rao and Rao, 1999
2	Assamicadine	$C_{16}H_{23}NO_5$ (*m/z* 309.3645)	253-255	*C. assamica*	Cheng et al., 1989
3	Axillarine	$C_{18}H_{27}NO_7$ (*m/z* 369.4143)	205-207	*C. axillaris*	Crout, 1969
4	*β*-Sitosterol	$C_{29}H_{50}O$ (*m/z* 414.7164)	261-163	*C. incana*	Azam et al., 2013
5	Crocandine	$C_{16}H_{25}O_5$ (*m/z* 311.3774)	224-246	*C. candicans*	Mushtaq et al., 1979
6	Cropodine	$C_{19}H_{29}NO_6$ (*m/z* 327.3773)	226-228	*C. semperflorens*	Sharma and Hebborn, 1968
7	Crosemperine	$C_{19}H_{29}NO_6$ (*m/z* 367.4412)	117-118	*C. semperflorens*	Sharma and Hebborn, 1968
8	Crotafuran B	$C_{19}H_{14}O_5$ (*m/z* 322.3176)	534-535	*C. pallida*	Lin et al., 2006
9	Crotalarine	$C_{18}H_{27}NO_6$ (*m/z* 353.4148)	167-168	*C. burhia*	Uddin and Khanna, 1979
10	Crotalarine lactone	$C_{18}H_{27}NO_6$ (*m/z* 353.4143)	332-334	*C. aegyptiaca*	Roeder et al., 1993
11	Crotaleschenine	$C_{17}H_{25}O_5$ (*m/z* 323.3886)	142-143	*C. leschenaultii*	Smith et al., 1988
12	Crotananine	$C_{17}H_{25}NO_5$ (*m/z* 323.39)	174-175	*C. nana*	Smith et al., 1988
13	Crotmarine	$C_{20}H_{20}O_4$ (*m/z* 324.3762)	120-122	*C. madurensis*	Bhakuni and Chaturvedi, 1984
14	Crotmadine	$C_{20}H_{20}O_4$ (*m/z* 324.1361)	191-193	*C. madurensis*	Bhakuni and Chaturvedi, 1984
15	Crotmarine	$C_{20}H_{20}O_4$ (*m/z* 324.1124)	120-121	*C. madurensis*	Bhakuni and Chaturvedi, 1984
16	Crotasteroiridocin	$C_{39}H_{64}O_3$ (*m/z* 580.4851)	170–171	*C. emarginella*	Ahmed et al., 2014
17	Daucosterol	$C_{35}H_{60}O_6$ (*m/z* 576.8532)	166-168	*C. saharae*	Aissaoui et al., 2014
18	Diosmetin	$C_{16}H_{12}O_6$ (*m/z* 300.2654)	558-559	*C. saharae*	Aissaoui et al., 2014
19	Diosmin	$C_{28}H_{32}O_{15}$ (*m/z* 608.5452)	107-109	*C. saharae*	Aissaoui et al., 2014
20	Elliptone	$C_{20}H_{16}O_6$ (*m/z* 352.3434)	177-176	*C. burhia*	Uddin and Khanna, 1979
21	Fulvine	$C_{16}H_{23}NO_5$ (*m/z* 309.3616)	212-213	*C. fulva*	Schoental, 1963
22	Grantaline	$C_{18}H_{25}NO_6$ (*m/z* 351.3990)	219-220	*C. virgulata*	Smith and Culvenor, 1984
23	Grantianine	$C_{18}H_{23}NO_7$ (*m/z* 365.3823)	223-224	*C. virgulata*	Smith and Culvenor, 1984
24	Isovitexin	$C_{21}H_{20}O_{10}$ (*m/z* 433.5487)	237-239	*C. sessiliflora*	Yoo et al., 2004
25	Madurensine	$C_{18}H_{25}NO_6$ (*m/z* 351.3996)	175-176	*C. madurensis*	Le Roux et al., 2012
26	Monocrotaline	$C_{16}H_{23}NO_6$ (*m/z* 325.3612)	202-203	*C. retusa*	Nakka et al., 2013
27	Munchiwarin	$C_{30}H_{36}O_4$ (*m/z* 460.6127)	N.R	*C. trifoliastrum*	Yang et al., 1998
28	Nilgirine	$C_{17}H_{23}NO_5$ (*m/z* 321.3721)	127-128	*C. mucronata*	Atal et al., 1968
29	4',5,7-trihydroxy-3-methoxyflavone	$C_{16}H_{12}O_6$ (*m/z* 300.2623)	555.558	*C. madurensis*	Bhakuni and Chaturvedi, 1984
30	Retusamine	$C_{19}H_{25}NO_7$ (*m/z* 379.4094)	174-176	*C. retusa*	Wunderlich, 1967
31	Stigmasterol	$C_{29}H_{48}O$ (*m/z* 412.7123)	244-246	*C. incana*	Azam et al., 2013
32	Trimethoxychalcone	$C_{23}H_{24}O_6$ (*m/z* 397.5461)	484-486	*C. ramosissima*	Rao and Narukullah, 2007
33	3*β*-(2,3,4-Trihydroxy-*Z*-cinnamoyl)olean-5-ene-12,8-diol	$C_{39}H_{58}O_7$ (*m/z* 638.4222)	N.R.	*C. incana*	Azam et al., 2013
34	2-Amino-5-hydroxyhexanoic acid	$C_6H_{13}NO_3$ (*m/z* 397.5481)	158-159	*C. junceai*	Prasad et al., 2013
35	2',4',7-Trihydroxy-isoflavone	$C_{15}H_{10}O_5$ (*m/z* 270.7231)	273-275	*C. sessiliflora*	Yoo et al., 2004
36	2',4',5,7-Tetrahydroxy-isoflavone	$C_{15}H_{10}O_6$ (*m/z* 286.0534)	271-273	*C. sessiliflora*	Yoo et al., 2004
37	Trifolirhizin	$C_{22}H_{22}O_{10}$ (*m/z* 446.4223)	142-144	*C. saharae*	Aissaoui et al., 2014
38	Tropinons	$C_8H_{13}NO$ (*m/z*139.1976)	112-114	*C. goreensis*	Culvenor and Smith, 1961

Table 2: Medicinal importance of secondary metabolites isolated from genus *Crotalaria.*

Sr. No.	Name of compound	Secondary metabolite group	Medicinal use	References
1	Anacrotine	Alkaloid	Antispasmodic	Rao and Rao, 1999
2	Assamicadine	Pyrrolizidine alkaloid	Antioxidant	Cheng et al., 1989
3	Axillarine	Pyrrolizidine alkaloid	Glycosidase inhibitor	Wadood et al., 2013
4	*β*-Sitosterol	Phytosterol	Reduces benign prostatic hyperplasia and blood cholesterol	Kim et al., 2012
5	Crocandine	Pyrrolizidine alkaloid	Antioxidant, repair DNA damage	Mushtaq et al., 1979
6	Cropodine	Alkaloid	Immune modulator	Kresina, 1998
7	Crosemperine	Pyrrolizidine alkaloid	Antimicrobial, anticancer	Sharma and Hebborn, 1968
8	Crotafuran B	Pterocarpanoid	Anti-inflammatory	Lin et al., 2006
9	Crotalarine	Pyrrolizidine alkaloid	Antimicrobial, anti-inflammatory, anti-nociceptive	Saboon et al., 2015
10	Crotalarine lactone	Pyrrolizidine alkaloid	Antimicrobial, anti-inflammatory	Roeder et al., 1993
11	Crotaleschenine	Alkaloid	-	Smith et al., 1988
12	Crotananine	Pyrrolizidine Alkaloid	Antimicrobial	Ribeiro et al., 2018; Siddiqi et al., 1978
13	Crotasteroiridocin	Steroiridoid	Anti-inflammatory	Ahmed et al., 2014
14	Crotmarine	Polyketoid flavonoide	Antifungal activity against *Trichophyton mentagrophytes*	Bhakuni and Chaturvedi, 1984
15	Crotmadine	Isoflavan flavonoid	Antifungal activity against *Trichophyton mentagrophytes*	Bhakuni and Chaturvedi, 1984
16	Daucosterol	Steroid saponin	Anticancer	Aissaoui et al., 2014
17	Dihydroalpinum-isoflavone	Flavonoid	Antifungal	Bhakuni and Chaturvedi, 1984
18	Diosmin	Flavonoid	Anti-inflammatory, treats hemorrhoids, varicose veins, poor circulation in the legs, blood clots; antiulcer, anticancer, and relieve radicular pain	Abd El Hady et al., 2019
19	Diosmetin	Flavonoid	Anticancer agent acting as a weak tropomyosin receptor kinase B agonist	Aissaoui et al., 2014
20	Elliptone	Flavonoid	Anticancer, antimicrobial	Russell et al., 2017
21	4',5,7-trihydroxy-3-methoxyflavone	Polyketoid flavonoid	Antitumor, antineoplastic agent, antioxidant	Yang et al., 2010
22	Fulvine	Pyrrolizidine alkaloid	Rodenticide	Mattocks and Driver,1983
23	Grantaline	Alkaloid	Antioxidant	Smith and Culvenor, 1984
24	Grantianine	Alkaloid	Antimicrobial	Smith and Culvenor, 1984
25	Isovitexin	Flavone glycoside	Antioxidant, anticancer, anti-inflammatory, anti-hyperalgesic, neuroprotective	He et al., 2016
26	Madurensine	Alkaloid	Anticancer	Le Roux et al., 2012
27	Monocrotaline	Pyrrolizidine alkaloid	Used as a dye plant, colic remedy, relieve fever, anti-congenital syphilis, anti-malaria, anti-hallucination	Nakka et al., 2013; Estep et al., 1991
28	Munchiwarin	Chalcone flavonoid	Antioxidant, detoxifying agent	Narender et al., 2007
29	Nilgirine	Alkaloid	-	Atal et al., 1968
30	Retusamine	Alkaloid	Hepatoprotective, antimicrobial	Culvenor et al., 1976
31	Stigmasterol	Sterol (steroid derivative)	Maintain structure & physiology of cell membranes, lowers blood total & LDL cholesterol, maintains HDL, synthesizes progesterone	Weststrate and Meijer, 1998
32	3*β*-(2,3,4-Trihydroxy-*Z*-cinnamoyl)olean-5-ene-12,8-diol	Steroid	-	Azam et al., 2013
33	Trifolirhizin	Flavonoid	Anticancer, antiasthma,	Lu et al., 2016
34	Trimethoxychalcone	Chalcone	Anti-inflammatory effect on microglial cells of central nervous system	Lee et al., 2012
35	Tropinons	Alkaloid	Anticancer, analgesic, antibacterial	Kittakoop et al., 2014; Cushnie et al., 2014
36	2-Amino-5-hydroxyhexanoic acid	Amino acid	-	Prasad et al., 2013
37	2',4',7-Trihydroxy-isoflavone	Flavonoid	Anti-inflammatory	Yoo et al., 2004
38	2',4',5,7-Tetrahydroxy -isoflavone	Flavonoid	Antioxidant, Anti-inflammatory	Yoo et al., 2004

cannot be simply defined (Cannell, 1998). This diverse group of compounds is synthesized by algae, plants, animals and fungi (Tania et al., 2003). Some secondary metabolites isolated from plants are used as drugs, flavors, dyes, dietary supplements, phytonutrients and cosmetics (Guerriero et al., 2015). These have benzene ring having various hydroxyl groups; simple or

polymerized (Velderrain et al., 2014). Now a day these have become of great interest due to their anticancer property, and their uses in treatment of heart diseases (Ibrahim et al., 2012). Phenolic acids are mostly present in potato, spinach, orange, pear, blueberry, tea, coffee beans, cherry juice and cider (Balasundram et al., 2006; Gonthier et al., 2006). These are classified into simple and complex derivatives consisting of fused aromatic rings (Kulbat, 2016). These are very effective due to their physiological effects like cardio-protective, anti-inflammatory, anti-thrombotic, anti-artherogenic, antimicrobial and antioxidant (Balasundram et al., 2006). Various compounds, belonging to classes of secondary metabolites, isolated from genus *Crotalaria* are listed in table 1.

Alkaloids

It is the largest group of secondary metabolites; approximately more than 6,000 compounds exhibit alkaloid like properties (Dewey and Xie, 2014). Alkaloids have significant role for toxicity against pathogens and predators (Hartmann, 2007). These can also detoxify stress releasing oxygen species and act as antioxidants (Matsuura and Neto, 2014; Porto et al., 2014). These are important defense tools for organisms like amphibians (Toledo and Jared, 1995).

Terpenoids

Pine trees have volatile liquid 'terpentine' known as terpene that is the reason these compounds are called terpenoids (Yadav et al., 2014). Depending upon the number of basic isoprene unit, there are various classes as hemi-, mono-, sesqui-, di-, sester-, tri-, and tetra-terpenoids (carotenoids) (Heras et al., 2003). Their concentrations vary in different parts of plants like fruit, bark, root, and seed (Bhargava et al., 2013). These have been used by humans in food, development of biofuel, and in pharmaceutical and chemical industries (Tholl, 2015). These also act as defense tools in plants during stress conditions (Mazid et al., 2011; Tholl, 2006).

Coumarins

Coumarins (2*H*-1-benzopyran-2-one) consist of a large class of phenolic substances found in plants and are made of fused benzene and α-pyrone rings (Aoyama et al., 1992). There are four main coumarin sub-types: the simple coumarins, furanocoumarins, pyranocoumarins and pyrone-substituted coumarins (Jain and Joshi, 2012). These are found at high levels in some essential oils, particularly cinnamon bark oil (7,000 mg L^{-1}), cassia leaf oil (up to 87,300 mg L^{-1}) and lavender oil (Lake, 1999). More than 1,300 coumarins have been identified as secondary metabolites from plants, bacteria, and fungi (Iranshahi et al., 2009). Some of these coumarin derivatives have been found useful in photochemotherapy, antitumor, anti-HIV therapy (Manfredini et al., 1997), as central nervous system (CNS)-stimulants, antibacterial, anticoagulants (Wattenberg et al., 1979; Valgas et al., 2007), antifungal, as antioxidants and dyes (Mazzone et al., 2015; Barker et al., 1971).

Steroids

The addition of different chemical groups at different positions on backbone leads to the formation of many different types of steroidal compounds including sex hormones like progesterone and testosterone, the anti-inflammatory steroids like corticosteroids, cardiac steroids like digoxin and digitoxin, animal steroids like cholesterol and steroidal glycosides (Benveniste, 1986). Plant steroids possess many interesting medicinal, pharmaceutical and agrochemical activities like antitumor, immunosuppressive, hepatoprotective and antibacterial (Yokota, 1997). The first steroid was isolated from shark liver oil but later on found to be present in almost all living organisms (Jovanovic et al., 2015). Cholesterol is one of the classes of steroids (Moss, 1989).

MEDICINAL IMPORTANCE OF PLANT'S SECONDARY METABOLITES

Some plants or products isolated from them have been and are still used to treat infections, health disorders or diseases (Michael, 2015). The levels and activities of a number of plant secondary metabolites are known to increase in response to increase in stress (Makkar et al., 2009). Phenolic compounds could be an important part of the plants defense system against pests and diseases including root parasitic nematodes (Mazid et al., 2011). For centuries, in India, snakeroot (*Rauvolfia serpentina*) is used as medicine due to its sedative consequences (Kong et al., 2003). Tulsi (*Ocimum sanctum*) is useed as a cure for bronchitis, vomiting and fever (Gupta et al., 2002). Kojic acid comprise antibacterial properties and employed for the cure of skin diseases and as a skin whitening agent is a part of several fungal species particularly *Aspergillus oryzae* (Yabuta, 1924). Augmentin is used as a broad-spectrum antibiotic (Butler, 2004). Discodermolide is a polyketide extracted from marine sponge (*Discodermia dissolute)*, which has antitumor and immunosuppressive activities (Gunasekera et al., 1990). Medicinal importance of secondary metabolites obtained from different species of genus *Crotalaria* is listed in table 2.

CONCLUSION

The genus *crotalaria*, considered as one of the largest genera having about 600 species, contains a variety of compounds such as phenols, alkaloids, steroids, flavonoids and fatty acids. In the present study, 38 compounds belonging to different secondary metabolite groups isolated from 23 species of *crotalaria* and their medicinal importance has been reported. Most of these compounds belong to alkaloid group of secondary metabolites, the remaining belong to flavonoid, saponin and steroid groups. These are medicinally important due to having antispasmodic, antioxidant, immune modulator, antimicrobial, anticancer, anti-inflammatory, anti-nociceptive, antifungal, antiulcer, antitumor, antineoplastic, anti-hyperalgesic, anti-pyretic, anti-asthma, neuroceptive and hepatoprotective activities etc.

REFERENCES

Abd El Hady, W.E., Mohamed, E.A., Soliman, O.A.E. and El-Sabbagh, H.M. 2019. *In vitro-in vivo* evaluation of chitosan-PLGA nanoparticles for potentiated gastric retention and anti-ulcer activity of diosmin. *International Journal of Nanomedicine*, 14: 7191-7213.

Ahmed, B., Al-Howiriny, T.A. and Mossa, J.S. 2014. Crotasteroiridocin, A new steroiridoid from *Crotalaria emarginella* and its anti-inflammatory activity. *Zeitschrift fur Naturforschung*, 61: 629-635.

Aissaoui, M., Leon, F., Brouard, I., Benayache, F. and Benayache, S. 2014. Secondary metabolites from *Crotalaria saharae* (Fabaceae). *Scholars Research Library*, 1: 186-189.

Anulika, N.P., Ignatius, E.O., Raymond, E.S., Osasere, O.I. and Abiola, A.H. 2016. The chemistry of natural products: Plant secondary metabolites. *International Journal of Technology Enhancement and Emerging Engineering*, 4: 2347-4289.

Aoyama, Y., Katayama, T., Yamamoto, M., Tanaka, H. and Kon, K. 1992. A new antitumor antibiotic product, demethylchartreusin: Isolation and biological activities. *The Journal of Antibiotics*, 45: 875-878.

Atal, C.K., Sawhney, R.S., Culvenor, C.C.J. and Smith, L.W. 1968. Nilgirine, a new *Crotalaria* alkaloid of senecionine type lacking the 1′-carbon atom. *Tetrahedron Letters*, 9(54): 5605-5608.

Azam, Z., Moni, F., Hamiduzzaman, M., Masud, M.E. and Hussan, C.M. 2013. Two cinnamoyl triterpenes and steroids from *Crotalaria incana* (Fabaeceae). *Research Journal of Phytochemistry*, 15: 1819-3471.

Balasundram, N., Sundram, K. and Samman, S. 2006. Phenolic compounds in plants and agri-industrial by-products: Antioxidant activity, occurrence, and potential uses. *Food Chemistry*, 99: 191-203.

Barker, W.M., Hermodson, M.A. and Link, K.P. 1971. 4-Hydroxycoumarins: Synthesis of the metabolites and some other derivatives of warfarin. *Journal of Medical Chemistry*, 14: 167-169.

Beech, E., Rivers, M. and Oldfield, S. 2017. Global tree search: The first complete global database of tree species and country distributions. *Journal of Sustainable Forestry,* 36(5): 454-489.

Benveniste, P. 1986. Sterol biosynthesis. *Plant Physiology*, 37: 275-308.

Bhakuni, R. and Chaturvedi, C. 1984. Constituents of *Crotalaria madurensis. Journal of Natural Products*, 4: 585-591.

Bhargava, V.V., Patel, S.C. and Desai K.S. 2013. Importance of terpenoids and essential oils in chemotaxonomic approach. *International Journal of Herbal Medicine*, 1: 14-21.

Butler, M.S. 2004. The role of natural product chemistry in drug discovery. *Journal of Natural Products*, 21: 41-53.

Butler, M.S. 2005. Natural products to drugs: natural product derived compounds in clinical trials. *Natural Products Report*, 22: 162-195.

Cannell, R.J.P. 1998. How to approach the isolation of a natural product. In: Cannell, R.J.P. (ed.). Methods in Biotechnology. 4. Natural Products Isolation. Humana Press, Totowa, New Jersey, USA, pp. 1-51.

Cheng, Y.L., Chu, T.T., Cui, Y., Cheng, J. and Roeder, E. 1989. Assamicadine, a new Pyrrolizidine alkaloid from *Crotalaria assamica*. *Journal of Natural Products*, 5: 1153-1155.

Crout, D.H.G. 1969. Structures of axillarine and axillaridine, novel pyrrolizidine alkaloids from *Crotalaria axillaris* Ait. *Journal of Chemical Society C: Organic*, 20: 1379-1385.

Culvenor, C.C. and Smith, L.W. 1961. The alkaloids of *Crotalaria goreensis* 7β-Hydroxy-1-methylene-8β- and 7β-Hydroxy-1-methylene-8α-pyrrolizidine. *Australian Journal of Chemistry*, 2: 284-294.

Culvenor, C.C., Edgar, J.A., Jago, M.V., Qutteridge, A., Peterson, J.E. and Smith, L.W. 1976. Hepato and pneumotoxicity of pyrrolizidine alkaloids and derivatives in relation to molecular structure. *Chemico-Biological Interactions,* 12(3): 299-324.

Cushnie, T.P., Cushnie, B. and Lamb, A.J. 2014. Alkaloids: An overview of their antibacterial, antibiotic-enhancing and antivirulence activities. *International Journal of Antimicrobial Agents*, 44(5): 377-386.

Daimon, H. 2006. Traits of the genus *Crotalaria* used as a green manure legume on sustainable cropping systems. *Japan Agriculture Research Quarterly*, 4: 299-305.

Daniel, D., Urban, S. and Roessner, U. 2012. A historical overview of natural products in drug discovery. *Metabolites*, 2: 303-336.

Dayan, F.E., Cantrell, C.L. and Duke, S.O. 2009. Natural products in crop protection. *Bioorganic* & *Medicinal Chemistry*, 17: 4022-4034.

Debbab, A., Aly, A.H., Lin, W.H. and Proksch, P. 2010. Bioactive compounds from marine bacteria and fungi. *Microbial Biotechnology*, 3(5): 544-563.

Devendra, B.N., Srinivas, N. and Solmon, K.S. 2012. A comparative pharmacological and phytochemical analysis of *in vivo* & *in vitro* propagated *Crotalaria* species. *Asian Pacific Journal of Tropical Medicine*, 3: 37-41.

Dewey, R. and Xie, J. 2014. Molecular genetics of alkaloid biosynthesis in *Nicotiana tabacum*. *Phytochemistry*, 94: 10-27.

Estep, J.E., Lame, M.W., Morin, D., Jones, A.D., Wilson, D.W. and Segall, H.J. 1991. [14C]monocrotaline kinetics and metabolism in the rat. *Drug Metabolism and Disposition,* 19(1): 135-139.

Gomes, G.S., Silva, G.S., Silva, D.L.S., Oliveira, R.R. and Coceicao, G.M. 2018. Botanical composition of Fabaceae family in the Brazilian Northeast, Maranhao, Brazil. *Asian Journal of Environment & Ecology,* 6(4): 1-10.

Gonthier, M.P., Remesy, C., Scalbert, A., Cheynier, V., Souquet, J.M., Poutanen, K. and Aura, A.M. 2006. Microbial metabolism of caffeic acid and its esters chlorogenic and caftaric acids by human faecal microbiota *in vitro*. *Biomedicine & Pharmacotherapy*, 60: 536-540.

Guerriero, G., Berni, R., Armando, J., Sanchez, M., Apone, F., Eslam, M., Ahmad, A., Abdulrahman, A., Cantini, C., Cai, G., Hausman, J.F., Siddiqui, K.S., Teresa, S.M., Sotomayor, H. and Faisal, M. 2015. Plant metabolism for improved metabolite biosynthesis and enhanced human benefit. *Molecules*, 20: 12698-12731.

Gunasekera, S., Gunasekera, M., Longley, R. and Schulte, G. 1990. Discodermolide: a new bioactive polyhydroxylated lactone from the marine sponge *Discodermia dissoluta*. *Journal of Organic Chemistry*, 55: 4912-4915.

Gupta, S., Prakash, J. and Srivastava, S. 2002. Validation of traditional claim of Tulsi, *Ocimum sanctum* Linn.as a medicinal plant. *Indian Journal of Experimental Biology*, 40: 765-773.

Hartmann, T. 2007. From waste products to ecochemicals: research of plant secondary metabolism. *Phytochemistry*, 68: 31-46.

He, M., Min, J.W., Kong, W.L., He, X.H., Li, J.X. and Peng, B.W. 2016. A review on the pharmacological effects of vitexin and isovitexin. *Fitoterapia,* 115: 74-85.

Heras, B., Rodríguez, B., Bosca, L. and Villar, A.M. 2003. Terpenoids: Sources, structure elucidation and therapeutic potential in inflammation. *Medicinal Chemistry*, 3: 53-67.

Ibrahim, M.H., Jaafar, Z.E., Karimi, E. and Ghasemzadeh, A. 2012. Primary, secondary metabolites, photosynthetic capacity and antioxidant activity of the Malaysian herb Kacip Fatimah (*Labisia pumila* Benth) exposed to potassium fertilization under greenhouse conditions. *International Journal of Molecular Science*, 13: 15321-15342.

Iranshahi, M., Askari, M., Sahebkar, A. and Hadjipavlou-Litina, D. 2009. Evaluation of antioxidant, anti-inflammatory and lipoxygenase inhibitory activities of the prenylated coumarin umbellipenin. *DARU Journal of Pharmaceutical Sciences,* 17(2): 99-103.

Jabeen, S., Hanif, M.A., Khan, M.M. and Qadri, R.W.K. 2014. Natural products sources and their active compounds on disease prevention: A review. *International Journal of Chemical and Biochemical Sciences,* 6: 76-83.

Jain, P.K. and Joshi, H. 2012. Coumarin: chemical and pharmacological profile. *Journal of Applied Pharmaceutical Science*, 2(6): 236-240.

Jovanovic, S.S., Petri, E.T., Klisuric, O.R., Szecsi, M. and Kovacevic, R. 2015. Antihormonal potential of selected D-homo and D-secoestratriene derivatives. *Steroids,* 97: 45-53.

Judd, W.S., Cambell, C.S., Kellogg, E.A., Stevens, P.F. and Donoghue, M.J. 2002. Plant Systematics: A Phylogenetic Approach (3rd Ed.). Sinauer Associates Inc., USA.

Katrria, S., Shrivastava, B., Kaur, D. and Sharma, P. 2012. Antiinflammatory and antiociceptive activities of *Crotalria burhia* Buch.-Ham whole plant. *Indian Journal of Natural Products and Resources*, 3(2): 189-196.

Kim, T.H., Lim, H.J., Kim, M.S. and Lee, M.S. 2012. Dietary supplements for benign prostatic hyperplasia: An overview of systematic reviews. *Maturitas*, 73(3): 180-185.

Kittakoop, P., Mahidol, C. and Ruchirawat, S. 2014. Alkaloids as important scaffolds in therapeutic drugs for the treatments of cancer, tuberculosis, and smoking cessation. *Current Topics in Medical Chemistry*, 14(2): 239-252.

Knaggs, R. 2003. The biosynthesis of shikimate metabolites. *Natural*

Product Reports, 20: 119-136.

Kong, J.M., Goh, N.K., Chia, L.S. and Chia, T.F. 2003. Recent advances in traditional plant drugs and orchids. *Acta Pharmacologica Sinica*, 24(1): 7-21.

Kresina, T.F. (ed.).1998. Immune Modulating Agents. Marcel Dekker Inc., New York.

Kulbat, K. 2016. The role of phenolic compounds in plant resistance. *Biotechnology of Food Science*, 80(2): 97-108.

Lake, B. 1999. Synthesis and pharmacological investigation of 4-hydroxy coumarin derivatives and shown as anti-coagulant. *Food Chemistry and Toxicology*, 3: 412-423.

Lalitha, B.R., Lakshmi, S.M. and Kumar, S. 2011. Evaluation of anti-diarrhoeal activity of methanolic extract of *Crotalaria juncea* Linn. In albino Wistar rats. *Advances in Pharmacological Sciences,* 2: 66-70.

Le Roux, K., Prinsloo, L.C., Hussein, A.A. and Lall, N. 2012. A micro-Raman spectroscopic investigation of leukemic U-937 cell treated with *Crotalaria agatiflora* Schweinf and the isolated compound madurensine. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 95: 547-554.

Lee, Y.H., Jeon, S.H., Kim, S.H., Kim, C., Lee, S.J., Koh, D., Lim, Y., Ha, K. and Shin, S.Y. 2012. A new synthetic chalcone derivative, 2-hydroxy-3',5 5'- trimethoxychalcone (DK-139), suppresses the Toll-like receptor 4-mediated inflammatory response through inhibition of the Akt/NF-κB pathway in BV2 microglial cells. *Experimental and Molecular Medicine*, 44: 369-377.

Lin, M.W., Sao, L.T.T., Huang, L.J., Kuo, S.C., Weng, J.R., Ko, H.H., Lin, C.N., Lee, M. and Wang, J.P. 2006. Inhibition of lipopolysaccharide-stimulated NO production by crotafuran B in RAW 264.7 macrophages involves the blockade of NF-kappaB activation through the increase in IkappaBalpha synthesis. *Toxicology and Applied Pharmacology*, 1: 108-115.

LPWG (Legume Phylogeny Working Group). 2017. A new subfamily classification of the Leguminosae based on a taxonomically comprehensive phylogeny. *Taxonomy*, 66(1): 44-77.

Lu, X., Ma, J., Qiu, H., Yang, L., Cao, L. and Shen, J. 2016. Anti-proliferation effects of trifolirhizin on MKN45 cells and possible mechanism. *Oncology Reports*, 36(5): 2785-2792.

Makkar, H.P.S., Norvsambuu, T., Lkhagvatseren, S. and Becker, K. 2009. Plant secondary metabolites in some medicinal plants of Mongolia used for enhancing animal health and production. *Tropicultura*, 27: 159-167.

Manfredini, S., Daniele, S., Ferroni, R., Bazzanini, R., Vertuani, S., Hatse, S. and Balzarini, J.E. 1997. Retinoic acid conjugates as potential antitumor agents: synthesis and biological activity of conjugates with Ara-A, Ara-C, 3(2H)-furanone, and aniline mustard moieties. *Journal of Medical Chemistry*, 40: 3851-3857.

Matsuura, H.N. and Neto, M.R. 2014. Oxidative stress and production of bioactive monoterpene indolealkaloids: biotechnological implications. *Biotechnology*, 36: 191-200.

Mattocks, A.R. and Driver, H.E. 1983. A comparison of the pneumotoxicity of some pyrrolic esters and similar compounds analogous to pyrrolizidine alkaloid metabolites, given intravenously to rats. *Toxicology*, 27(2): 159-177.

Mazid, M., Khan, T.A. and Mohammad, F. 2011. Role of secondary metabolites in defense mechanisms of plants. *Biology and Medicine*, 3(2): 232-249.

Mazzone, G., Malaj, N., Galano, A., Russo, N. and Toscano, M. 2015. Antioxidant properties of several coumarin–chalcone hybrids from theoretical insights. *Royal Society of Chemistry Advances*, 5: 565-575.

Melo, Y., Silvia, R. and Alve, M. 2010. Anatomy of extra floral nectaries in Fabaceae from dry-seasonal forest in Brazil. *Botanical Journal of the Linnean Society*, 163: 87-98.

Meriem, A.I., Brouard, F., Leon, F. and Benayache, S. 2014. Secondary metabolites from *Crotalaria saharae* (Fabaceae). *Der Pharmacia Lettre*, 6(1): 186-189.

Michael, W. 2015. Modes of action of herbal medicines and plant secondary metabolites. *Medicines*, 2: 251-286.

Moss, G. 1989. Nomenclature of steroid. *Pure and Applied Chemistry*, 61: 1783-1822.

Mushtaq, A., Suri, S., Suri, O.P. and Atal, C.K. 1979. New pyrrolizidine alkaloids from *Crotalaria candicans*. *Phytochemistry*, 18: 1413-1415.

Nakka, S., Kumar, B.V. and Devendra, B.N. 2013. Analysis of pyrrolizidine alkaloid from *Crotalaria retusa*. *Der Pharma Chemica*, 5(6): 6-11.

Narender, T., Reddy, K.P., Shweta, Srivastava, K., Mishra, D.K. and Puri, S.K. 2007. Total synthesis of munchiwarin, a triprenylated chalcone from *Crotalaria medicagenia*. *Organic Letters,* 9(26): 5369-5372.

Newman, D.J. 2008. Natural products as leads to potential drugs: An old process or the new hope for drug discovery? *Journal of Medicinal Chemistry*, 51: 2589-2599.

Parvaiz, M., Hussain, K., Khalid, S., Hussnain, N., Iram, N. and Azhar, A.M. 2014. Medicinal importance of *Glycyrrhiza glabra* L. (Fabaceae family). *Global Journal of Pharmacology*, 1: 8-13.

Porto, D.D., Matsuura, H.N. and Vargas, L.R.B. 2014. Shoot accumulation kinetics and effects on herbivores of the wound-induced antioxidant indole alkaloid brachycerine of *Psychotria brachyceras*. *Natural Product Communications*, 9: 29-32.

Prasad, J., Singh, V.K., Shrivastava, A., Chaturvedi, U., Bhatia, G., Arya, K.R., Awasthi, S.K. and Narender, T. 2013. Antidyslipidemic and antioxidant activity of an unusual amino acid (2-amino-5-hydroxyhexanoic acid) isolated from the seeds of *Crotalaria juncea*. *Phytomedicine*, 1: 15-19.

Rahman, A.H.M.M. and Parvin, M.I.A. 2015. Taxonomic studies on the family Fabaceae (weeds) at Rajshahi University Campus. *Plant*, 3(3): 20-25.

Raj, L.J.M., Britto, S.J., Prabhu, S. and Senthilkumar, S.R. 2011. Identification of agronomically valuable species of *Crotalaria* based on phenetics. *Agriculture and Biology Journal of North America*, 50: 2151-7517.

Rao, M.S. and Narukulla, R. 2007. A new trimethoxychalcone from *Crotalaria ramosissima*. *Fitoterapia*, 78(6): 446-447.

Rao, M.S. and Rao, P.S. 1999. Anacrotine: A crotanecene alkaloid from *Crotalaria trifoliastrum*. *Fitoterapia*, 70(4): 449-450.

Ribeiro, M., Simoes, L.C. and Simoes, M. 2018. Biocides. In: Reference Module in Life Sciences. Encyclopedia of Microbiology (4th Ed). Elsevier Inc., USA, pp. 478-790.

Roeder, E., Sarg, T., El-Dahmy, S. and Ghani, A.A. 1993. Pyrrolizidine alkaloids from *Crotalaria aegyptiaca*. *Phytochemistry*, 5: 1421-1423.

Russell, D.A., Fong, W.J.S., Twigg, D.G., Sore, H.F. and Spring, D.R. 2017. Stereocontrolled semisyntheses of elliptone and 12aβ-hydroxyelliptone. *Journal of Natural Products*, 80(10): 2751-2755.

Saboon, Bibi, Y., Arshad, M., Ahmad, N., Riaz, I. and Chaudhari, S.K. 2015. An insight into medicinal and ethnopharmacological potential of *Crotalaria burhia*. *Asian Pacific Journal of Tropical Disease,* 5(7): 511-514.

Scarim, C.B., Vizioli, E.O., Santos, J.L.D. and Chin, C.M. 2017. NSAIDs and natural products interactions: Mechanism and clinical implications. *Journal of Immunology and Clinical Research,* 4(2): 1-11.

Schoental, R. 1963. Alkaloidal constituents of *Crotalaria fulva* Roxb.: Fulvine and its N-oxide. *Australian Journal of Chemistry*, 16(2): 233-238.

Sharma, M. and Kumar, A. 2013. Leguminosae (Fabaceae) in tribal medicines. *Journal of Pharmacognosy and Phytochemistry*, 2: 276-283.

Sharma, R.K. and Hebborn, P. 1968. Antitumor and antimicrobial screening of crosemperine, the otonecine ester occurring in *Crotalaria semperflorens*. *Journal of Medicinal Chemistry*, 11(3): 620-621.

Siddiqi, M.A., Suri, K.A. and Atal, C.K. 1978. Genus *Crotalaria*: Part xxxiv. Cronaburmine a new pyrrolizidine alkaloid from *Crotalaria nana* Burm. *Indian Journal of Chemistry (B)*, 16B(12): 1132-1133.

Smith, J.A.E., Gable, W.R., Mackay, M.F., Suri, O.P.A. and Culvenor, C.C.J. 1988. Crotaleschenine, an alkaloid of *Crotalaria leschenaultia*. *Australian Journal of Chemistry*, 4: 429-436.

Smith, L.W and Culvenor, C.J. 1984. Grantianine and grantaline, alkaloids

of *Crotalaria virgulata*. *Phytochemistry*, 23(2): 473-474.

Tania, S., Costa, A., Roberto, F., Humberto, R., Silveira, D. and Marcos, A. 2003. Secondary metabolites. *International Journal of Molecular Sciences*, 24: 1311-1331.

Tholl, D. 2006. Terpene synthases and the regulation, diversity and biological roles of terpene metabolism. *Plant Biology*, 9: 297-304.

Tholl, D. 2015. Biosynthesis and biological functions of terpenoids in plants. *Advances in Biochemical Engineering / Biotechnology*, 148: 63-106.

Tiwari, R. and Rana, C.S. 2015. Plant secondary metabolites. *International Journal of Engineering Research and General Science*, 3: 3861-3863.

Toledo, R. and Jared, C. 1995. Cutaneous granular glands and amphibian venoms. *Comparative Biochemistry and Physiology*, 111: 1-29.

Uddin, A. and Khanna, P. 1979. Rotenoids in tissue cultures of *Crotalaria burhia*. *Planta Medica*, 6: 181-183.

Umerie, S.C., Okonkwo, I.F., Nwadialor, N.A. and Okonkwo, J.C. 2010. Studies on the oil and nutritive value of seeds of *Crotalaria retusa* L. (Fabaceae). *Pakistan Journal of Nutrition*, 9: 912-914.

Valgas, C., de Souza, S.M., Smania, E.F.A. and Smania Jr, A. 2007. Screening methods to determine antibacterial activity of natural products. *Brazilian Journal of Microbiology,* 38: 369-380.

Velderrain, G.R., Carlos, H.P., Medrano, A.W., Zavala, J.F.A., Chen, C.Y.O., Sanches, M.R., Garcia, H.A., Parrilla, E.A. and Aguilar, G.A.G. 2014. Phenolic compounds: Their journey after intake. *Food and Function,* 5: 189-197.

Wadood, A., Ghufran, M., Jamal, S.B., Naeem, M., Khan, A., Ghaffar, R. and Asnad. 2013. Phytochemical analysis of medicinal plants occurring in local area of Mardan. *Biochemistry and Analytical Biochemistry,* 2(4): 1-4.

Watkins, R., Wu, L., Zhang, C., Davis, R.M. and Xu, B. 2015. Natural products-based nanomedicines. *International Journal of Nanomedicine*, 10: 6055-6074.

Wattenberg, L.W., Lam, K.T. and Fladmoe, A.V. 1979. Inhibition of chemical carcinogen-induced neoplasia by coumarins and α-angelicalactone. *Journal of Medical Chemistry*, 39: 1651-1654.

Weststrate, J.A. and Meijer, G.W. 1998. Plant sterol enriched margarines and reduction of plasma total and LDL cholesterol concentrations in normocholesterolaemic and mildly hypercholesterolaemic subjects. *European Journal of Clinical Nutrition*, 52(5): 334-343.

Wunderlich, J.A. 1967. The crystal structure of retusamine, -bromo-D-camphor-trans-sulphonate monohydrate. *Acta Crystallographica*, 23: 846-855.

Yabuta, T. 1924. The constitution of kojic acid, a γ-pyrone derivative formed by *Aspergillus oryzae* from carbohydrates. *Journal of the Chemical Society Transactions*, 125: 575-587.

Yadav, N., Yadav, R. and Goyal, A. 2014. Chemistry of terpenoids. *Medicinal Chemistry*, 45: 272-278.

Yang, C., Lotte, H., Wagner, H., Mouly, B.C., Avn, A.R. and Rao, P.S. 1998. Munchiwarin, a prenylatedchalcone from *Crotalaria trifoliastrum*. *Journal of Natural Products*, 10: 1274-1276.

Yang, Y., Zhou, X., Xiao, M., Hong, Z., Gong, Q., Jiang, L. and Zhou, J. 2010. Discovery of chrysoeriol, a PI3K-AKT-m TOR pathway inhibitor with potent antitumor activity against human multiple myeloma cells *in vitro*. *Journal of Huazhong University of Science and Technology (Medical Sciences),* 30(6): 734-740.

Yokota, T. 1997. The structure, biosynthesis and functions of brassinosteroids. *Trends in Plant Science*, 2: 137-143.

Yoo, H.S., Lee, J.S., Kim, C.Y. and Kim, J. 2004. Flavonoids of *Crotalaria sessiliflora*. *Archives of Pharmaceutical Research*, 27: 544-546.