REVIEW ARTICLE

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records of natural products

Phytochemistry and Pharmacology of Genus *Indigofera:* A Review

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Abstract: In this review, the existing literature data on the phytochemical and biological studies of the genus *Indigofera* are outlined with 71 references. Up till now, 65 compounds were secluded from various species of genus *Indigofera*. The chemical components are mostly terpenoids, flavonoids and nitro group containing compounds, together with steroids and others. The metabolites and crude extracts of the genus *indigofera* were found to exhibit various bioactivities including, antimicrobial, insecticidal, phytotoxic, antiulcergenic, hepatotoxic, teratogenic and cytotoxicity. Other constituents isolated from the genus *Indigofera* displayed inhibitory activity against the enzyme lipoxygenase and gastrointestinal activity. This review represents a brief description of the total Phytochemical and Pharmacological activities of genus *Indigofera* as well as chemotaxonomic classification of chemical constituents.

Keywords: Phytochemistry; *Indigofera;* bioactivity; pharmacology.

1. Introduction

Plants play a major role in the maintenance of life on the planet earth. They convert simple substances into complicated entities producing chemicals that are essential for human health. Medicinal plants have been used as folk medicines by the people throughout the world [1]. From ancient time man has used plants for food, shelters and to treat various common diseases. Even, nowadays medicinal plants are widely used in a variety of products; such as pharmaceutical, dermaceutical and nutraceuticals products. The greatest demand and wide use of herbal products have become a major trade in the world by developing expensive medicines to treat various diseases. One of the ancient health core known to the human beings are the herbal medicines. In this modern era 20% of all prescription drugs still come from trees, shrubs or herbs, which are either directly obtained from the plant extracts or synthesized to mimic compounds derived from plants. The rural population of both Asian and African countries routinely uses herbs for the treatment of various diseases. In fact, many of the prescriptions used by traditional healers provide effective treatment for a variety of diseases but the role of the indigenous systems of medicine in national health programs has remained a subject of controversy. One group of professionals use the traditional system of medicine and claim that they have a remedy for almost every disease that exist, while modern system of medicine on the other hand rejects completely the entire indigenous system. The truth somewhat lies in between, and it is a need of the day to learn from each other's experiences, which

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would be essential for the well-being of human beings. It is therefore necessary that user of modern system of medicine must take an unbiased scientific look at the herbal concoctions to evaluate their usefulness for specific diseases. Before the discovery of antibiotics, infections were the most common 55 causes of mortality. Quinine alkaloid was the first chemical compound isolated from the bark of *Cinchona* tree (*Cinchona officinalis*) that effectively controlled certain fevers caused by malaria [1].

In the 18th century a folk medical practitioner Reverend Edward Stone used to treat fever by utilizing the bark of white willow (*Salix alba*) with the same bitter taste like *Cinchona.* The principle responsible for controlling fever in willow bark was salicin, an analog of salicylic acid. Other closely related natural compounds were successively discovered and found to relieve fever, pain, swelling, gout, rheumatic fever and arthritis. A drug reserpine isolated from roots of *Rauvolfia serpentinae* was used in the treatment of hypertension, snakebite and mental illness. Examples of other valuable drugs from natural sources includes opiates and pilocarpine used for glaucoma, dry-mouth syndrome while vincristine and vinblastine obtained from *Catharanthus roseus* prescribed for pediatric leukemia and Hodgkin's disease respectively, which shows that medicinal plants have the valuable source of medicinal agents since time immemorial and Still continue to play a dominant role in primary health care. Keeping in view the importance of medicinal plants a review on genus indigofera was hoarded to further highlight the medicinal potential of various species of this genus to the researcher. The genus *Indigofera,* contains 300 species. All of these are herbs or shrubs, dispersed all through the tropical regions of the earth. In Pakistan it is epitomized by 24 species [2].

The genus *Indigofera* belongs to family, Fabaceae which is ranked the third largest family of the blossoming plants after Orchidnaceae and Asteraceae with approximately 650 genera and 18000 different species. The family in overall is characterized by the pod (legume) type of fruit developing from a single carpal with marginal placentation. The family Fabaceae is divided in to three sub-families (*Caesalpiniodeae*, *Mimosoideae*, *Faboideae*). In Pakistan, the species of genus *Indigofera* are found in mountainous areas of North West Frontier Province, Azad Jammu and Kashmir, Northern Areas of Dir, from 1500 to 3000 meters [3]. In India, some species are available in Himalayas, Kasi Afghanistan and W. China [4]. Fast-growing when young but slowing with age [5]. Tolerates light shade [6]. A tall shrub, 2.5m, covered bristly white hairs, copiously branched shrub with short imaripinnate, leaflets 9-33; flowers in axillary racemes, in erect often almost stalk less Oleg and Rix, (1985) bright red or rosy or radish purple [3,4] standard petal sessile, stamens diadelphous; pod cylindrical 10-12 seeded [3] have a vanillas cent [7]; flowers are mostly 6-10 mm; calyx bristal haired, with lobes as tubes; bracts minute. Leaves and leaflets very variable, leaflets elliptic to oblanceolate, mostly 4-12mm, with white hairs. Pod 1.3-2.5cm, straight, hairless [8].

In reported works extensive work has been done on various species of the genus *Indigofera*. For instance, *Indigofera oblongifolia* has shown its antimicrobial [9] hepatoprotective [10] and lipoxygenase inhibitory activity [10]. Abubakar *et al*. has reported the snake-venom neutralizing bustle of *Indigofera pulchra* [11]. Antioxidant and free radical scavenging and anti-dyslipidemic actions of *Indigofera tinctoria* has also been reported [12,13]. *Indigofera emarginella* has shown in-vitro antimalarial action against *Plasmodium falciparum*. Chakrabarti *et al.* have reported the antidiabetic activity of *Indigofera mysorens* [14]. Whole plant is used in hepatitis, whooping cough [3] antispasmodic [15], tonic [16], the extract prevents the development of hypoglycemia in the mouse [17]; the plant leaves, flowers and tender shoots are cooling and demulcent, they are used in the form of leprosery and tumorous infection. The leaves are applied to abscesses. The roots are chewed in toothache and lethargy [16]. The alcoholic extract of the dried shoots has reported anti-inflammatory action [18]; the root bark is chomped in the mouth to relieve the abdominal pain [7]; leaves, bark and roots have antibacterial potency [19, 15].

2. Chemical Constituents

Compounds 1-65 are the known chemical constituents isolated from the genus *Indigofera* (Table 1, Figure 1). They are commonly flavonoids, especially, flavonoids glycosides. Many lignin and a few of other constituents including alkaloids, steroids, fatty acids containing amino group.

1. Flavonoidal compounds isolated from the *Indigofera* species; among the reported compounds, (**1-29**) are flavonoids isolated mainly from *I. hebepetala, I. arrecta, I. pseudotinctoria, I. suffruticosa, I. hetrantha* Wall, *I. tinctoria, I. zollingeriana* Miq, *I. hebepetala* Benth and *I. kirilowi*.
2. Nitro group containing compounds; which included compounds (**30-34**) were isolated from *I. linnaei, I. endecaphylla, I. Suffruticosa, I. spicata* and *I. endecaphylla.*
3. Amide; among the reported compounds (**35-37**) were isolated from *I. pseudomonas, I. tinctoria, I. spicata* and *I. endecaphylla.*
4. Steroidal compounds; which included compound (**38-42**) were isolated from *I. pseudotinctoria* and *I. kirilowi.*
5. Keto compounds; which further included compounds (**43-45**) containing keto group were isolated from *I. pseudotinctoria* and *I. longeracemosa.*
6. Keto flavonoid; included one compound (**46**) was isolated from *I. suffruticosa.*
7. Lignin; the compounds (**47-48**) were isolated from *I. pseudotinctoria* belongs to lignin's.
8. Alkaloids; the compound (**49**) was isolated from *I. tinctoria, I. suffruticosa* and *I. truxillensis* Kunth.
9. Terpenoids; the compounds (**50-51**) were isolated from *I. longeracemosa* Boiv. ex. Baill. and *I. hetrantha.*
10. Miscellaneous compounds; (**52-53**) were isolated from *I. longeracemosa, I. oblongifolia* Forssk. and *I. hetrantha.*
11. Toxic constituents (**54-56**) were isolated from of *I. spicata*
12. The three known rotenoids (**57-59**) were isolated from *I. spicata.*
13. A known chalcone (**60**) was isolated from *I. spicata*
14. A known Nitropropanoyl compound (**61**) was isolated from *I. suffriticosa*
15. Bezofurans (**62-63**) were isolated from *I. microcorpa.*
16. A Cerebroside (**64**) was isolated from *I. heterantha*
17. An Ester (**65**) was isolated from *I. heterantha*

The data given above revealed chemotaxonomic classification of the chemical constituents in various species of genus *indigofera*.

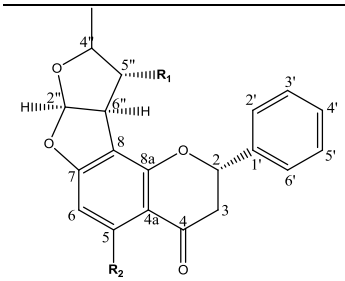
3. Biological Activities

The genus *Indigofera* is known for the medicinal important due to a rich source of secondary metabolites such as flavonoids, triterpenoids, lignins and steroids. Based on structure activity relationship the biological activities of different class of compounds isolated from various species of the genus *Indigofera* are highlighted below. Indirubin isolated from *I. suffruticosa* proved to be excellent inhibitor in mice against lewis lung carcinoma and walker 256 carcinosarcoma [59]. Indispicine isolated from both *I. spicata* and *I. endecaphylla* (Posses good hepatotoxic and teratogenic activity [61]. While bovinocidin obtained from *I. endecaphylla* has showed moderate activity against mycobacterium tuberculosis [62]. Louisfieserone isolated from *I. suffruticosa* has antibacterial stroke against vague gram-positive and gram-negative microorganisms [65]. The isolated compound Hetranthin A displayed in *vitro* lipoxygenase inhibitory potential with an IC_{50} value of 2.1 μg/mL [28]. Fat food treated with a mixture of semiglabrin and pseudosemiglabrin (20:80) keeps significant reductions in plasma triglycerides (60%), as well as completes cholesterol (19%), along with an upsurge in high density lipoprotein (8%) [29]. Indigo, a 2,2′-bisindole alkaloid is a main component of *I. tinctoria*, used as a blue dye. A 2,3′-isomer of indigo and insignificant component of *I. tinctoria*, indirubin, was documented as the active ingredient present in "Dang Gui Lu Hui" pills, containing eleven outmoded Chinese medicinal herbs. "Dang Gui Lu Hui" pills which are used in outmoded Chinese medicine to cure chronic myelogenous leukemia [40-41].

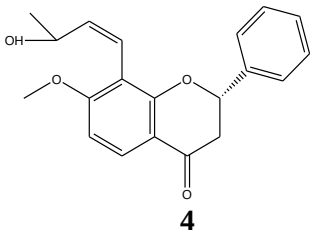
Table 1. Compounds isolated from the species of the genus *Indigofera*

S. No.	Compound Name	Source	Ref
Flavonoidal compounds			
1	(+)-5″-deacetylpurpurin	*I. spicata*	[20]
2	(+)-5-methoxypurpurin	*I. spicata*	[20,21]
3	(+)-purpurin	*I. spicata*	[22, 23]
4	(2S)-2,3-dihydrotephroapollin C	*I. spicata*	[20]
5	(2S)-2,3-dihydrotephroglabrin	*I. spicata*	[20]
6	(2S)-7-methoxy-8-(3-methoxy-3- methylbut-1-enyl) flavanone	*I. spicata*	[42]
7	Kaempferitrin	*I. arrecta*	[24]
8	Kaempferol 3,7diarabinoside	*I. hebepetala*	[25]
9	Kaempferol 7-alloside	*I. hebepetala*	[25]
10	Triflin;2´´-O-β-L-ramnopyranosyl,7-O-β-L-arabinofuranoside	*I. hebepetala*	[26]
11	Triflin;6´´-O-β-L-ramnopyranosyl,7-O-β-L-arabinofuranoside	*I. hebepetala*	[26]
12	Formononetin	*I. pseudotinctoria*	[20]
13	Afromosin	*I. pseudotinctoria*	[20]
14	Genistein	*I. pseudotinctoria*	[20]
15	Rutin	*I. kirilowi*	[27]
16	7,4'-Dihydroxy-3'-methoxy isoflavone	*I. pseudotinctoria*	[20]
17	Formononetin-7-O-β-D-glucoside	*I. pseudotinctoria*	[20]
18	Kaempferol-3-O-rutinoside	*I. kirilowi*	[27]
19	Quercetin-3-O-glucosidase	*I. kirilowi*	[27]
20	Louisfieserone	*I. suffruticosa*	[67]
21	Hetranthin A	*I. hetrantha*Wall.	[28]
22	Hetranthin B	*I. hetrantha*Wall.	[28]
23	Glabretephrin	*I. tinctoria*	[29]
24	Semiglabrin	*I. tinctoria*	[29]
25	Pseudosemiglabrin	*I. tinctoria*	[29]
26	Flavonol glycoside	*I. tinctoria, I. zollingeriana*. *I. hebepetala* Benth. ex Baker	[30,31]
27	Quercetin	*I. aspalathoides Vahl ex DC.*	[32]
28	Kaempferol	*I. aspalathoides Vahl ex DC.*	[32]
29	kaempferol 5-O-b-D-glucopyranoside	*I. aspalathoides Vahl ex DC.*	[32]
Nitro group containing compounds			
30	Endecaphyllin A_1	*I. linnaei*	[33]
31	Hiptagin	*I. endecaphylla*	[33]
32	3-Nitropropanoates;2,3,4,6-tetrkis-(3-nitropropanoyl)-β -D-glucopyranose	*I. suffruticosa* and *I. linnaei*	[33]
33	Endecaphyllin	*I. endecaphylla*	[33]
34	3-Nitropropanoic acid, Et ester	*I. endecaphylla*	[33]
Amide			
35	Indigoidin	*I. pseudomonas*	[34]
36	Indigotin	*I. tinctoria*	[35]
37	(S)-Indispicine	*I. spicata* and *I. endecaphylla*	[36]
Steroidal compounds			
38	β –Sitosterol	*I. pseudotinctoria*	[20]

S. No.	Compound Name	Source	Ref
39	Daucosterol	*I.pseudotinctoria*	[20]
40	Lupeol	*I. kirilowi*	[28]
41	5-[(E)-2-(4-hydroxyphenyl] benzene-1,3-diol	*Indigoferalinnaei*, Ali	[37]
42	Gitoxin	*Indigoferalinnaei*, Ali	[37]
Keto compounds			
43	12-Oleanen-3,11- dione	*I. pseudotinctoria*	[20]
44	12-Oleanen-3,11-dione	*I. pseudotinctoria*	[20]
45	3β-acetoxy-12-oleanen-11-one	*I. pseudotinctoria*	[20]
Keto flavonoids			
46	Louisfieserone	*I. suffruticosa*	[39]
Lignin			
47	Isoliquiritigenin	*I. pseudotinctoria*	[20]
48	Maackiain	*I. pseudotinctoria*	[20]
Alkaloids			
49	Indigo, 2,2′-bisindole alkaloid	*I.tinctoria*, *I.suffruticosa*and *I. truxillensis* Kunth.	[40-42] [43]
Terpenoids			
50	Indigoferabietone	*I. longeracemosa*Boiv. ex. Baill.	[44]
51	Two monoterpene glycosides,	*I. hetrantha*	[45]
Miscellaneous compounds			
52	Indigin	*I. oblongifolia*Forssk.,	[46]
53	Indigoferic acid	*I. oblongifolia*Forssk.	[46]
Toxic constituents of I. spicata			
54	Indospicine	*I. spicata*	[28,47,48] [50,50]
55	Canavanine	*I. spicata*	[28-50]
56	3-nitropropanoic acid	*I. spicata*	[28-50]
Rotenoids			
57	cis-(6aβ,12aβ)-hydroxyrotenone	*I. spicata*	[51,52]
58	rotenone	*I. spicata*	[52,53]
59	Tephrosin	*I. spicata*	[52,54]
Chalcone			
60	(+)-tephropurpurin	*I. spicata*	[55]
Nitropropanoyl			
61	[2,3,4,6-tetra (3-nitropropanoyl) α-D-glucopyranose]	*I.suffruticosa*	[56]
Benzofuran			
62	2-(2'-hydroy-4'-methoxypheyl)-3-methyl-6-methoxy benzo[b] furan	*I. microcorpa*	[57]
63	2-(2'-hydroy-4'-methoxypheyl)-3-methyl-5,6-dioxmethyl-ene-benzo[b] furan	*I. microcorpa*	[57]
Cerebroside			
64	Indigoferamide-A	*I. heterantha*	[69]
Ester			
65	Indigoferate	*I. heterantha*	[70]



1 $\mathbf{R_1}$ = OH, $\mathbf{R_2}$= H
2 $\mathbf{R_1}$ = $OCOCH_3$, $\mathbf{R_2}$ = OCH_3
3 $\mathbf{R_1}$ = $OCOCH_3$, $\mathbf{R_2}$ = H



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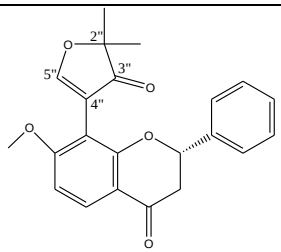

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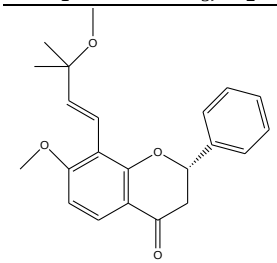

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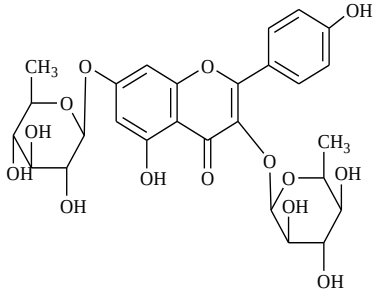

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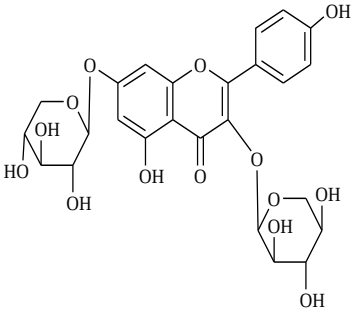

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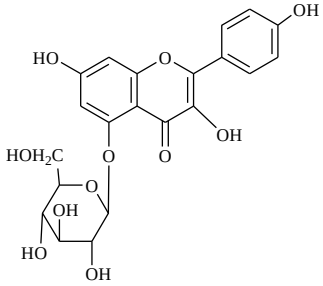

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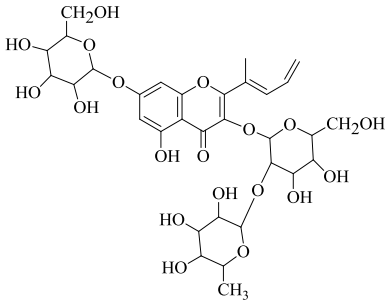

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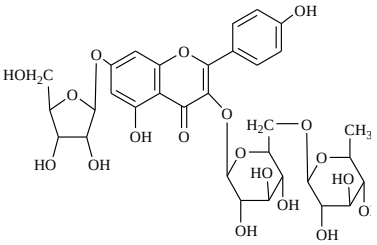

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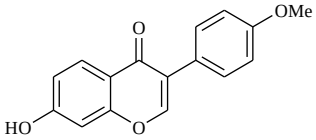

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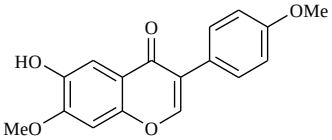

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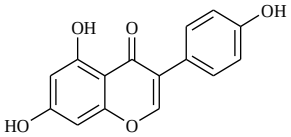

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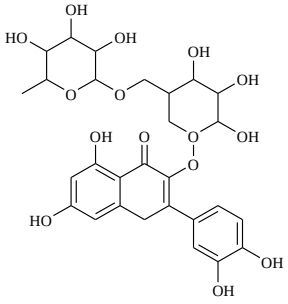

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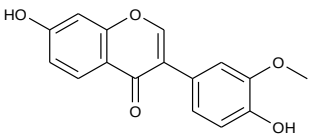

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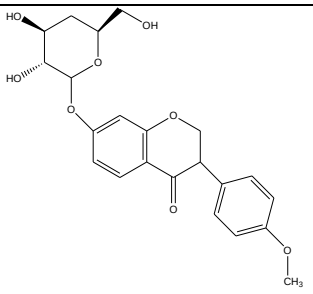

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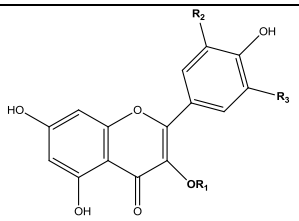

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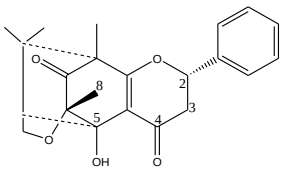
19 Glu OH H18



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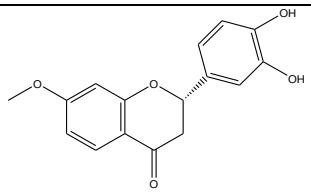

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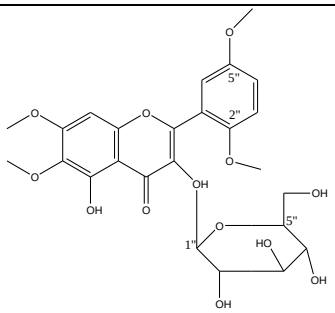

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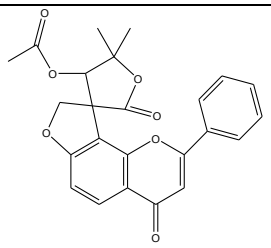

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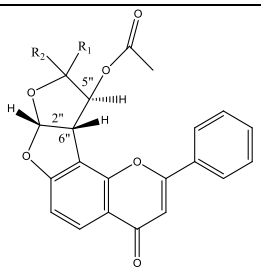

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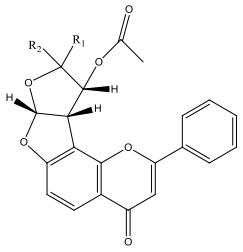

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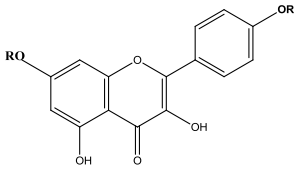

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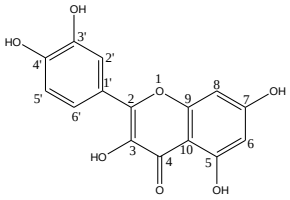

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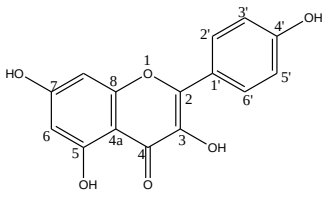

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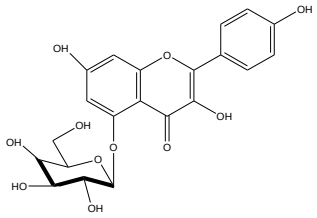

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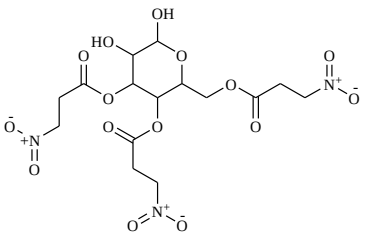

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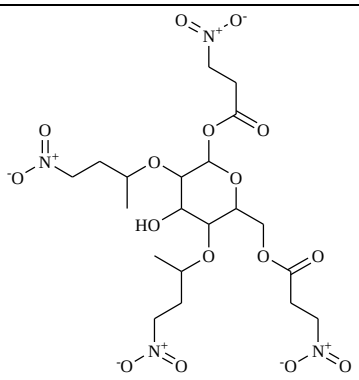

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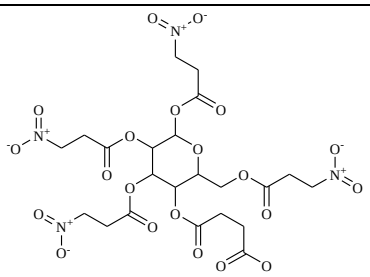

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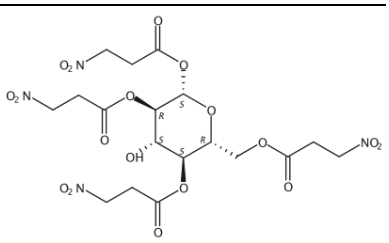

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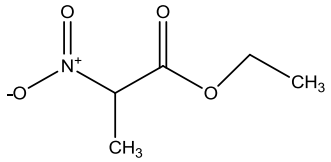

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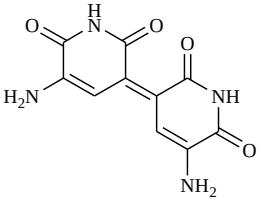

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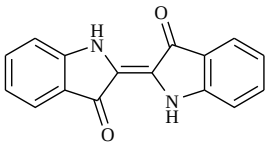

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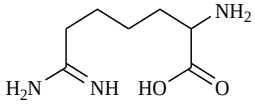

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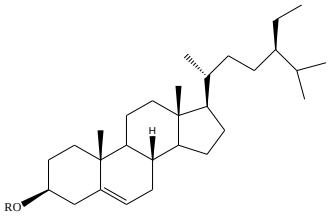

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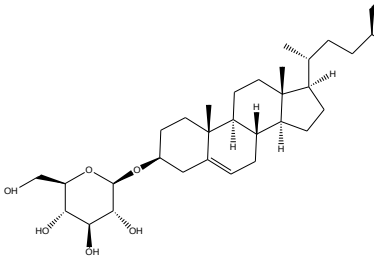

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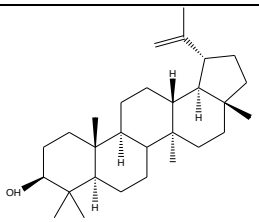

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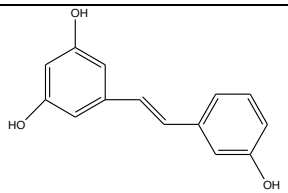

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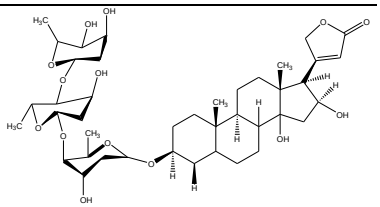

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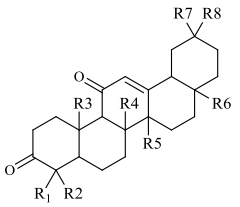
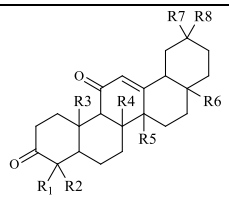


R_1 = R2 = R3 = R4 = R5 = R6 =R7 = R8 = CH_3

43



R_1 = R2 = R3 = R4 = R5 = R6 =R7 = R8 = CH_3

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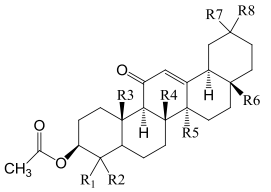

R_1 = R2 = R3 = R4 = R5 = R6 =R7 = R8 = CH_3

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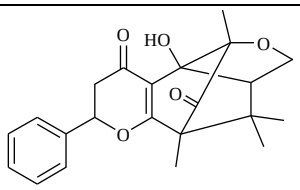

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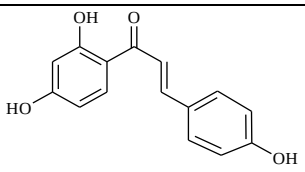

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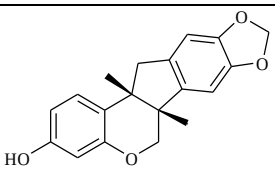

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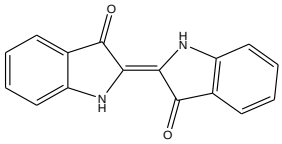

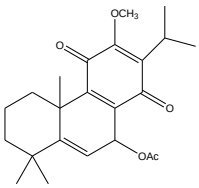

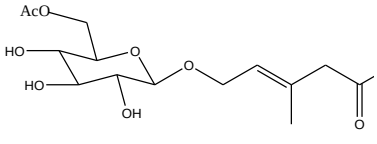

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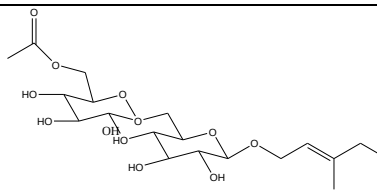

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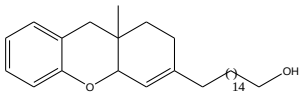

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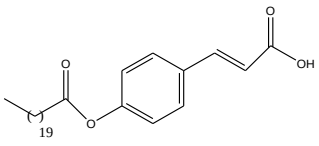

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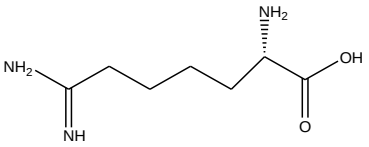

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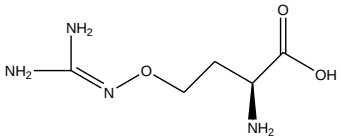

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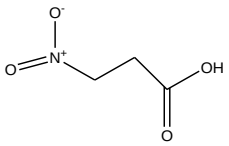

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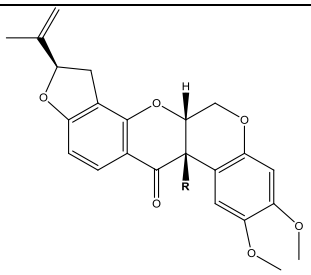
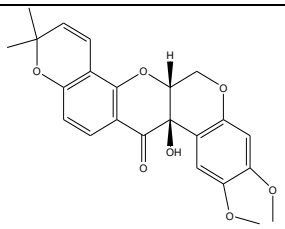


57 R= OH
58 R= H



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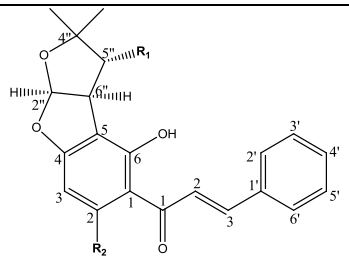
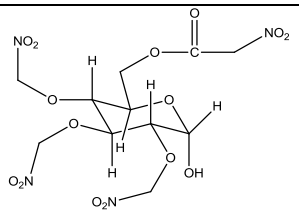


R$_1$= $OCOCH_3$
R$_2$= OCH_3
60



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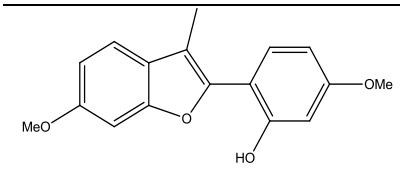

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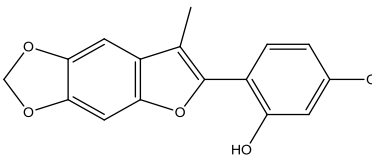

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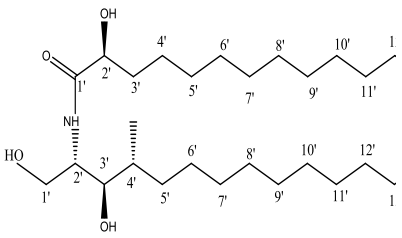

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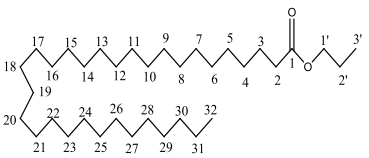

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Figure 1. Structure of chemical compounds in *Indigofera* species

Indigo has also been testified as an isolate of *I. suffruticosa* and *I. truxillensis* Kunth [42] [43]. This compound was shown to increase levels of nitric oxide (NO) and tumor necrosis factor-α (TNF-α) in addition to showing cytotoxicity against LM-2 breast adenocarcinoma and LP07 lung adenocarcinoma cells with IC_{50} values of 0.9 and 1.4 μg/mL, respectively [43]. In adding, indigo pretreatment in rats (2 mg/kg, p.o.) erstwhile to ethanol-induced gastric ulcer formation exhibited gastro defensive effects of about 80% suppression of the gastric lesions, when matched to a negative control (with no pretreatment) [42]. The component *I. bietone* with antifungal activity against *Candida albicans*, has been isolated from *I. longeracemosa* Boiv. ex. Baill [44]. The various crude sub fractions of extract of seeds of *I. heterantha* divulged phytotoxic and antifungal action [63] as well as antimicrobial and insecticidal abilities [64]. *I. bietone* also displayed robust activity against *Mycobacterium tuberculosis* with a minimum inhibitory concentration (MIC) value of 0.38 μg/μL, after duration of 21-day incubation period [44]. The MIC value of test compound is the lowest concentration that stopovers the observable growth of bacteria after an overnight incubation period [64] [66]. In addition, this compound showed antibacterial activity against *Proteus vulgaris*, *Escherichia coli* and *Staphylococcus aureus*, with MIC values of 1.5, 0.9, and 0.5 μg/μL, respectively, using the disk diffusion method [44].

Two monoterpene glycosides secluded from *I. heterantha*, were barbed out to exhibit *in vitro* lipoxygenase inhibition [45]. Both Indigin and indigoferic acid retain lipoxygenase inhibitory action and indigoferic acid also show weak butyrylcholinesterase (BChE) [46]. A lignin besides two acylphloroglucinols isolated from *I. hetrantha*, also revealed lipoxygenase inhibitory activity [58]. Indospicine and canavanine; (arginine inhibitors), and another toxic compound, 3-nitropropanoic acid in the leaves and seeds of this species [21] [48] [49] [50]. Indospicine was found to be teratogenic and to persuade abortion in pregnant animals [67-68]. The various components isolated from the *I. heterantha* revealed inhibitory activity against the enzyme lipoxygenase [38]. The aqueous acetone extract of *I. colutea, I. macrocalyx, I. pulchra, I. nigritana* and *I. tinctoria* bared significant antioxidant activity [59]. 3-Nitropropionate is the toxic substance of *indigofera* [60]. Some species of the genus *Indigofera* such as *I. heterantha* is used as herbal medicine as well as folk medicine to treat gastrointestinal disorder and abdominal pain [58]. The various crude extracts of *I.tinctoria* showed anti hyperglycemic, antibacterial, cytotoxicity, antidiabetic, anti inflamatory, anti epilective, anti hepatoprotective, antihelmenthic, antinoceptive, antiproliferative and antidyslipidemic activities [68]. The methanolic crude extract of *I. heterantha* roots exposed antidiabetic and antioxidant activity [71].

4. Conclusions

Although a large numbers of species of genus *Indigofera* are distributed all over the world, among, these few species were investigated. Phytochemical studies on the plants of this genus had led to the isolation of 65 compounds including terpenoids, flavonoids, lignins, Nitro group containing compounds, steroids and others etc. The chemical constituents and crude extracts of some species of genus *Indigofera* were found to possess different biological activities. Based on the literature survey the genus has high medicinal importance. Keeping in view the above mentioned literature survey the biological importance of genus *Indigofera* revealed that chemical exploitation of various species were found to retain different potential biological activities. Thus, much attention should be paid to *Indigofera* species for further discovery of novel phytochemicals and evaluation of their pharmacological activities. This will help to cope with various diseases by introducing novel therapeutic agents to world health community.

Competing Interests

Authors have declared that no competing interests exist.

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