



## ***Murraya Koenigii*: An Updated Review**

Vandana Jain\*<sup>1</sup>, Munira Momin<sup>1</sup>, Kirti Laddha<sup>2</sup>

<sup>1</sup> Oriental College of Pharmacy, Sector-2. Plot 4,5,6, Near Sanpada Railway station, Sanpada(W), Navi Mumbai 400705

<sup>2</sup> University Institute of Chemical Technology, Pharmaceutical division,  
Matunga (E), Mumbai 400 019

**Corresponding author:** Dr. Vandana Jain Oriental College of Pharmacy, Sector-2. Plot 4,5,6, Near Sanpada Railway station, Sanpada(W), Navi Mumbai 400705

*Medicinal plants or their bioactive compounds have been utilized by developing countries for primary and traditional healthcare system since very long period of time. In several ancient systems of medicine including Ayurveda, Siddha and Unani, Murraya koenigii, a medicinally important herb from mainly Asian origin has vast number of therapeutic applications such as in bronchial disorders, piles, vomiting, skin diseases etc. The medicinal utilities have been described especially for leaf, stem, bark and oil. The well studied pharmacology and phytochemistry of M. koenigii and therapeutic potential of this plant needs to be compiled in form of review. The present review incorporates the description of M. koenigii, its phytochemical constituents and various pharmacological activities of isolated compounds as well as bioactivity of extract studies carried out by various numbers of laboratories. In addition to that, it highlights its potential to be the important nutraceutical for diabetes and cardioprotection.*

**KEY WORDS:** *Murraya koenigii* , review, phytochemistry, biological activity

### **Introduction**

*Murraya koenigii*, commonly known as *curry leaf* or *kari patta* in Indian dialects, belonging to Family Rutaceae which represent more than 150 genera and 1600 species<sup>1</sup>. *Murraya Koenigii* is a highly values plant for its characteristic aroma and medicinal value. It is an important export commodity from India as it fetches good foreign revenue. A number of chemical constituents from every part of the plant have been extracted. The most important chemical constituents responsible for its intense characteristic aroma are P-gurjunene, P-caryophyllene, P-elemene and O-phellandrene. The plant is rich source of carbazole alkaloids<sup>2</sup>. Bioactive coumarins, acridine alkaloids and carbazole alkaloids from family Rutaceae were reviewed by Ito<sup>3</sup>. *M. koenigii* is widely used in Indian cookery for centuries and have a versatile role to play in traditional medicine. The plant is credited with tonic and stomachic properties. Bark and roots are used as stimulant and externally to cure eruptions and bites of poisonous animals. Green leaves are eaten raw for cure of dysentery, diarrhoea and for checking vomiting. Leaves and roots are also used traditionally as bitter, anthelmintic, analgesic, curing piles, inflammation, itching and are useful in leucoderma and blood disorders<sup>4,5</sup>. Several systematic scientific studies are also being conducted regarding the efficacy of whole plant or its parts in different extract forms for the treatment of different diseases. *M. koenigii* contains a number of chemical constituents that interact in a complex way to elicit their pharmacodynamic response. A number of active constituents responsible for the medicinal properties have been isolated and characterized. This plant has been reported to have anti-oxidative, cytotoxic, antimicrobial, antibacterial, anti ulcer, positive inotropic and cholesterol reducing activities<sup>6-13</sup> Therefore the present review summarizes the available literature till date on isolation of phytoconstituents, biological activities of the isolated compounds and pharmacological actions of extracts along with the clinical studies.

### **Plant description and Habitate:**

The plant is distributed and cultivated throughout India. It is found wild from Sikkim to Garhwal, Bengal, Assam, Western Ghats and Travancore- Cochin. Propagation is done by seeds, which germinate freely under partial shade. Is also available in other part of Asian region like in moist forests of 500-1600 m height in Guangdong, S Hainan, S Yunnan (Xishuangbanna), Bhutan, Laos, Nepal, Pakistan, Sri Lanka, Thailand,

Vietnam. Together with South Indian immigrants, curry leaves reached Malaysia, South Africa and Réunion island. Outside the Indian sphere of influence, they are rarely found.

*M. koenigii* is an unarmed, semi deciduous aromatic shrub or small tree with slender but strong woody stem and branches covered with dark grey bark, leaves are imparipinnate, glabrous, and very strongly aromatic. Leaflets 9-25 or more, short stalked, alternate, gland dotted and strongly aromatic.



The stem of *M. koenigii* is an aromatic and more or less deciduous shrub or small tree upto 6 meters in height and 15 to 40 cm in diameter<sup>14</sup> The main stem is dark green to brownish. The bark of the stem can be peeled off longitudinally which exposes the white wood underneath. Flowers are small, white fragrant ebracteate, calyx deeply five cleft, pubescent. Petals five, free, whitish, glabrous and with dotted glands. Fruits occur in close clusters, small ovoid or sub-globose, glandular, thin pericarp enclosing one or two seeds having spinach green color.<sup>15</sup>

#### **Traditional Uses:**

Fresh leaves, dried leaf powder, and essential oil are widely used for flavouring soups, curries, fish and meat dishes, eggs dishes, traditional curry powder blends, seasoning and ready to use other food preparations. The essential oil is also utilized by soap and cosmetic aromatherapy industry.<sup>16</sup> Curry leaves are boiled with coconut oil till they are reduced to blanked residue which is then used as an excellent hair tonic for retaining natural hair tone and stimulating hair growth. It is traditionally used as a whole or in parts as antiemetics, antidiarrheal, febrifuge, blood purifier, antifungal, depressant, anti-inflammatory, body aches, for kidney pain and vomiting.<sup>17-29</sup>

#### **Phytochemistry:**

Mature leaves contains 63.2 % moisture, 1.15 % total nitrogen, 6.15 % fat, 18.92 % total sugars, 14.6 % starch, 6.8 % crude fiber, ash 13.06 %, acid insoluble ash 1.35 %, alcohol soluble extractive 1.82%, cold water (20°C) extractive 27.33% and a maximum of hot water soluble extractive 33.45%.<sup>30</sup> Constituents that have been stimulated the most interest includes a wide range of carbazole alkaloids, essential oil and carotenoids. The following major group of bioactive constituents summarizes the constituents of murraya. The figure 1 is a compilation of all important bioactive constituents with their chemical structure.

#### **Carotenoids:**

Leaves contain 9744 ng of lutein, 212 ng of  $\alpha$ -tocopherol and 183 ng of carotene/g of fresh weight.<sup>31</sup> 21.4 mg/100 g of total carotene, 7.1 mg/100 g of  $\beta$ -carotene is reported by Bhaskarachary *et. al.*<sup>32</sup> E. Siong Tee has reported 14570- $\mu$ g/100 g of total carotenoids in leaves as measured by HPLC. Out of total carotenoids, lutein content was 5252 and  $\beta$ -carotene content was 9328  $\mu$ g /g.<sup>33</sup>

#### **Carbazole alkaloids:**

##### **Leaves:**

Tachibana *et.al* has isolated 8, 10'-{3,3',11, 11'-tetrahydro-9,9' dihydroxy- 3,3',5, 8'-tetra methyl -3,3'-bis (4-methyl-3-pentenyl)}bis pyrano (3,2 a) carbazole (a dimeric carbazole alkaloid) from methylene chloride

extract of *M. koenigii* leaves together with six known alkaloids; koenimbine, O- methyl murrayamine, O-methyl mahanine, isomahanine and bismahanine and bispyrayafoline.<sup>34,35</sup> From dried leaves glycozoline,<sup>36</sup> 1-formyl -3 methoxy- 6-methyl carbazole and 6, 7- dimethoxy- 1- hydroxy- 3-methyl carbazole<sup>37</sup> was isolated. Koenigine, koenine, koenidine and (-) mahanine were isolated from acetone extract of leaves.<sup>(38)</sup> From the hexane extract of leaves Joshi *et.al* has isolated mahanimbine, isomahanimbine, koenimbidine and murrayacine.<sup>39</sup> Isomahanimbicine was isolated from petroleum ether extract of leaves of *M. koenigii* specifically collected in the month of February<sup>38</sup>. Euchrestine B, mahanine, mahanimbicine, mahanimbine<sup>35</sup>, bismurrayafoline E<sup>35,40</sup>, mahanimbicine, bicyclomahanimbicine<sup>41</sup>, cyclomahanimbicine bicyclomahanimbicine, mahanimbidine<sup>42</sup>, mukonicine<sup>43</sup>, 8, 8''- bis koenigine, new binary carbazole alkaloid along with its monomer koenigine<sup>44</sup> and a minor alkaloid mahanine<sup>45</sup> were identified and isolated from leaves of *M. koenigii*. Gupta *et.al* has reported the presence of murrayanine (0.32%), glycoside scopolin (0.25%), free glucose (3.5%) and ash (10.4%)<sup>46</sup>. Aerial part is reported to contain murrayanine and 8,8'' bis koenigine<sup>47</sup>. Petroleum ether extract of leaves was used to isolate carbazole alkaloids, mahanimbine (3,5-dimethyl-3-(4-methylpent-3-enyl)-11H-pyrano[5,6-a] carbazole)<sup>48</sup>. Methanolic extract of *M. Koenigii* was subjected to qualitative thin-layer chromatography and HPLC using different solvent system by Gupta *et.al*. Spectral analysis (IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and MS) was carried out to establish the structure. The structures of these 6-bioactive compounds confirmed as carbazole alkaloids- Mahanimbine, Girinimbine, Isomahanimbine, Murrayazoline, Murrayazolidine, and Mahanine, by the spectrometric data.<sup>49</sup>

### Stem:

From alcohol extract of stem bark Saha *et.al* has isolated koenigine- quinone A and koenigine quinone B, structures were established as 7- methoxy- 3 methyl carbazole- 1,4- quinone and 6, 7-dimethoxy-3-methyl carbazole-1, 4- quinone respectively<sup>50</sup>.

9- carbethoxy-3-methyl carbazole and 9- formyl -3- methyl carbazole were identified from *M. koenigii* by Chakraborty *et. al*<sup>51</sup>.

Me- 2- methoxy carbazole -3- carboxylate and 1- hydroxy -3- methyl carbazole were isolated from stem bark<sup>52</sup>. Mukonal, a probable biogenetic intermediate of pyrano carbazole alkaloid was detected in stem bark.<sup>53</sup>

From stem bark Murrayazolinol (a minor carbazole alkaloid)<sup>54</sup>, mahanimbicol<sup>55</sup>, murrayazolidine<sup>56, 57</sup>, murrayacinine<sup>58</sup>, mukonidine<sup>59</sup>, murrayazolinine<sup>60</sup>, murrayanine, girinimbine and mahanimbine<sup>61</sup>, girinimbicol and mahanimbicol<sup>62</sup> (possible biogenetic precursors of girinimbine and mahanimbine) has also been identified and isolated.

### Roots:

Murrayanol, murrayagetin, marmesin- 1''- O- rutinoside were isolated from root extract<sup>63</sup>. Three monomeric and five binary carbazole alkaloids named mukoenine- A, -B and C and murrastifoline -F. bis - 2- hydroxy- 3- methyl carbazole, bismahanine, bi koeniquinone- A and bismurrayaquinone A were isolated from root and stem bark<sup>64</sup>.

Koenoline (1- methoxy-3- hydroxy methyl carbazole) was isolated from the root bark<sup>65</sup>, Mukoline, mukolidine were isolated from the benzene extract of roots<sup>63</sup>. Roots were also found to contain girinimbine<sup>39, 66</sup>.

### Seeds:

Mahanimbine, girinimbine, koenimbine, isomahanine and mahanine were isolated from seeds of *M. koenigii* from Marassana, Sri Lanka<sup>67</sup>. 2- methoxy-3- methyl carbazole was isolated from petroleum ether extract of seeds<sup>68</sup>. Mandal *et.al* isolated three bioactive carbazole alkaloids, kurryam (I), Koenimbine (II) and koenine (III) with structural confirmation with 2D-NMR spectra<sup>69</sup>

### Fruits:

Mahanimbine and koenimbine were isolated from petroleum ether extract of fruits<sup>38,70</sup>. Isomahanine and murrayanol were isolated from fruits by Reisch *et. al* along with five previously reported carbazole alkaloids mahanimbine, murrayazolidine, girinimbine, koenimbine and mahanine<sup>71</sup>.

### Coumarin:

Indicolactone, anisoalctone and 2', 3' epoxy indicolactone (a furocoumarin lactone) were isolated from the seeds. This represents the first furocoumarin with a mono terpenoid lactone chain in the genus *Murraya*<sup>72</sup>.

Adebajo *et. al* has reported xanthotoxin, isobyanagelicol, byakangelicol and isogosferol as minor furocoumarins in seeds of *M. koenigii*<sup>73</sup>. Isoheraclenin, isoimperatonin, oxypeucedanin, isopimpinellin and bergaptan were isolated from seeds of Marassana village, Sri Lanka, suggesting it as a new chemical race<sup>74</sup>. A new coumarin galactoside marmesin- 1'-O- $\beta$ -D-galactopyranoside, osthol and umbelliferone were isolated from ethanol stem bark extract<sup>75</sup>. 3-(1,1-dimethyl allyl xanthyletin) was isolated from petroleum ether extract of stem bark of *M. koenigii*<sup>76</sup>.

#### Carbazole carboxylic acid:

Stem showed the presence of mukeic acid (1-methoxy carbazole-3-carboxylic acid)<sup>77</sup> and mukoeic acid<sup>78</sup>.

#### Lipids:

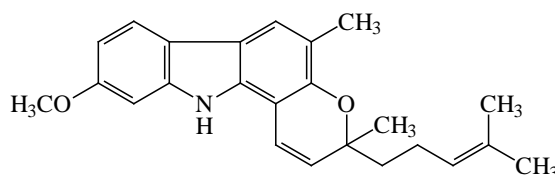
Lipid composition of seeds revealed 4.4% of total lipids of which 85.4% neutral lipids, 5.1% glycolipids and 9.5% phospho-lipids. Neutral lipids consisted of 73.9% triacylglycerol, 10.2% free fatty acids and small amounts of diacylglycerols, monoacylglycerols and sterols. Steryl glucoside and acylated sterylglucoside are major glycolipids. Phospholipids mainly consisted of phosphatidyl ethanolamine and lysophosphatidyl choline<sup>79</sup>.

#### Essential oil:

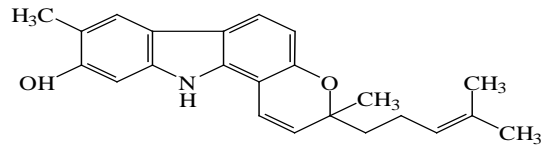
Tender leaves contain 0.8% oil as obtained by steam distillation. A number of reports are there on the essential oil composition of leaves obtained by steam distillation, solvent extraction or by fluid carbon dioxide extraction. The oil composition shows phenotypic and genetic variability in diverse origin germplasm lines of curry neem<sup>80-87</sup>. The chemical composition of the essential oil from leaves of *M. Koenigii* varies with variation in agronomic and geographical variation. The leaves oil of *Murraya koenigii* from Southern Nigeria<sup>88</sup> contains sesquiterpenes (89.1%). The major constituents were  $\beta$ -caryophyllene (20.5%), bicyclogermacrene (9.9%),  $\alpha$ -cadinol (7.3%), caryophyllene epoxide (6.4%),  $\beta$ -selinene (6.2%) and humulene (5.0%). The fresh leaves of *Murraya koenigii* from Dehradun<sup>89</sup> contains apinene (51.7%), sabinene (10.5%),  $\beta$ -pinene (9.8%),  $\beta$ -caryophyllene (5.5%), limonene (5.4%), bornyl acetate (1.8%), terpinen-4-ol (1.3%),  $\gamma$ -terpinene (1.2%) and  $\alpha$ -humulene (1.2%) as the major constituents.

The essential oil of leaves consists mainly of monoterpenoids and its oxygenated derivatives<sup>84</sup>. The major oil constituents are  $\beta$ -caryophyllene (35.8%),  $\beta$ -phellendrene (2.57%),  $\alpha$ -pinene (0.26%),  $\beta$ -elemene (0.18%) and  $\beta$ -thujene (4.12%) as determined by GC-MS of steam distillate. Other components are  $\alpha$ -caryophyllene (9.17%), cardinene (8.43%), selinene (8.88%), linalool (0.27%), trans ocimene (3.12%), gujunene (1.46%)<sup>80</sup>. Volatile oil obtained from flowers consists of 34.4% monoterpenoids and 43.9% of sesquiterpenoids. The major components are  $\beta$ -caryophyllene (24.2%), (E)- $\beta$ -Ocimene (18.0%) and linalool (8.0%)<sup>90</sup>.

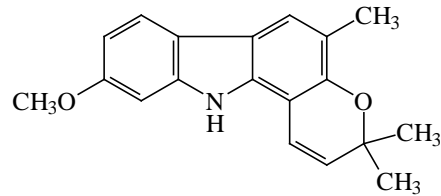
Volatile oil composition of the fruit of *M. Koenigii* has been first time reported by Awasthi *et. al*. As per their studies hydrodistillation of fruits of *Murraya koenigii* resulted in the isolation of 0.13% of oils (w/v) on fresh weight basis respectively. GC and GC-MS analysis resulted in the identification of 73 constituents comprising 98.8% of the oil, of which the major ones were caryophyllene oxide (10.3%),  $\beta$ -caryophyllene (8.5%), tridecanoic acid (8.2%), dehydroaromadendrene (8.0%), terpinen-4-ol (8.0%),  $\alpha$ -cadinol (7.3%), and (Z,E)-farnesol (5.7%)<sup>91</sup>.



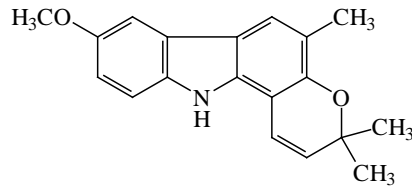
O- methyl mahanine



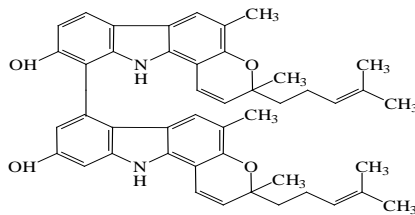
Isomahanine



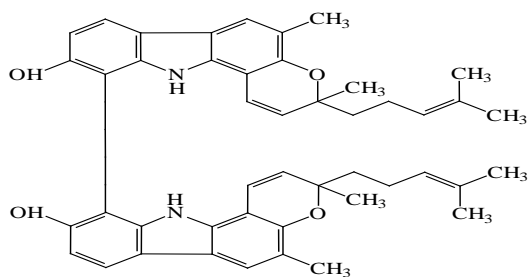
O- methyl murrayanine



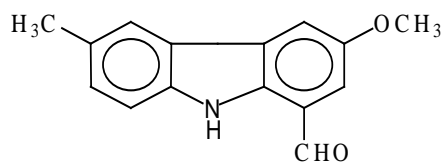
Koenimbine



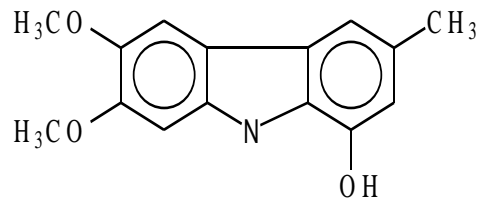
Bismahanine



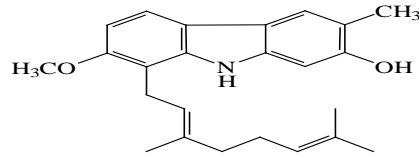
Bispyrafoline



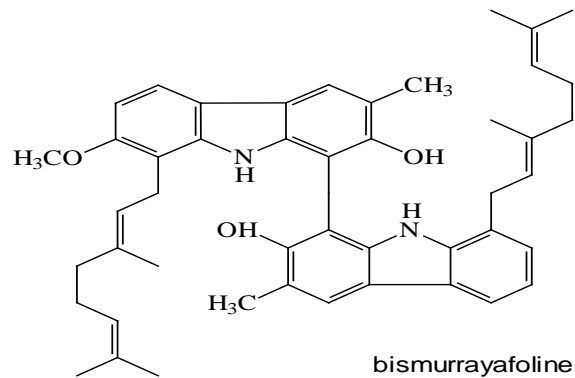
1-formyl 3-methoxy 6 methyl carbazole



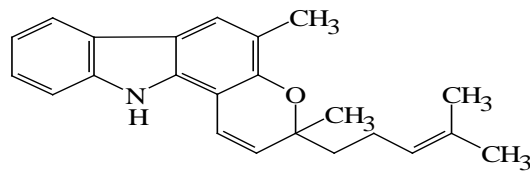
6,7-dimethoxy 1-hydroxy carbazole



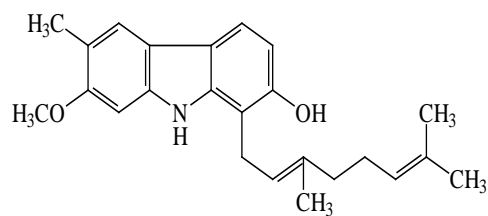
Euchrestine



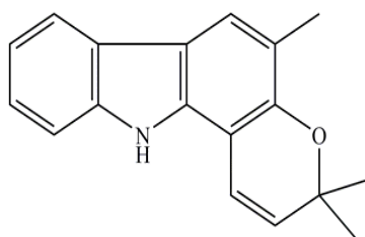
bismurrayafoline



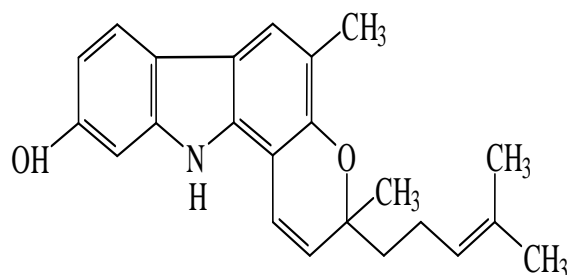
Mahanimbine



Murrayanol



Grinimbine



Mahanine

### Pharmacological activity profile of *M. koenigii*:

Several pharmacological activities and medicinal properties of various parts of *M. koenigii* are well known. Biological activity of *M. koenigii* is reported with the crude extracts and their different fraction form leaf, bark, roots, seed and oil. Although a number of compounds have been isolated from various parts of *M. koenigii*, a few of them have been studied for their biological activity as shown in Table no. 1

### Antioxidant and free radical-scavenging activity:

Antioxidant activity of carbazole alkaloids, one of the potential bioactives, has been reported by a number of workers.

The antioxidative properties of 12 carbazole alkaloids isolated from *M. koenigii* leaves were evaluated on the basis of Oil Stability Index (OSI) together with their radical scavenging ability against 1, 1-diphenyl, 2-picryl hydrazyl (DPPH). The OSI ratio of Euchrestine B (9.01), mahanine (10.4), isomahanine (8.81), bismahanine, bispyrayafoline and 8, 10'-{3,3', 11, 11'-terahydro-9, 9' dihydroxy- 3,3',5, 8'-tetra methyl – 3,3'-bis (4-methyl-3-pentenyl)} bis pyrano (3,2 a) carbazole were significantly higher than that of BHT. Antioxidant activity of mahanin was greater than that of  $\alpha$ -tocopherol. The scavenging activity in DPPH model was in the order bismahanine, bis pyrayafoline, euchrestine B, bismurrayafoline > mahanine > isomahanine, 8, 10'-{3,3', 11,11'-terahydro-9, 9' dihydroxy- 3,3', 5, 8'-tetra methyl – 3,3'-bis (4-methyl-3-pentenyl)} bis pyrano (3,2 a) carbazole with IC 50% ( $\mu$ M) 13.3, 13.85, 14.85, 14.97, 16.65, 24.0, 27.58 respectively<sup>34</sup>. Five carbazole alkaloids isolated from methylene chloride extract; Euchrestine B(I), bismurrayafoline E(II), mahanine(III), mahanimbicine(IV) and mahanimbine(V) which showed OSI value of the order I and III > tocopherol > BHT > II > IV, V, while in DPPH activity these carbazoles were in the order ascorbic acid > II > I, III and tocopherol > BHT > IV and V<sup>35</sup>.

Ramsewak *et. al* reported antioxidant activity of mahanimbine IC 50 (33.1  $\mu$ g/ml) by analysis of liposome oxidation model using fluorescence spectroscopy<sup>92</sup>. The alcohol-water (1:1) extract of curry leaves showed the highest antioxidant and free radical-scavenging activity. It reduced cytochrome c and ferric ion levels, chelated ferrous ions and inhibited ferrous sulfate: ascorbate-induced fragmentation and sugar oxidation of DNA<sup>93</sup>

Anti-peroxidative effect of alcoholic extract of *M. koenigii* in rat liver homogenate showed dose dependent effect. Study was carried out using ferrous sulphate-treated group, produced 405.69 unit of TBARS, which gradually decreases from 400.09 to 125.66 nmol/100 mg protein in a dose-dependent manner in the presence of *M. koenigii*<sup>94</sup> Gupta *et.al.* carried out comparative antioxidant activity between *M. koenigii*, Centella

asiatica, *Amaranthus* species and *Trigonella foenum-graecum*, the total antioxidant activity was found to be highest in *M. koenigii* (2 691.78  $\mu\text{mol}$  of one gram ascorbic acid sample) and least in *C. asiatica* (623.78  $\mu\text{mol}$  of one gram ascorbic acid sample)<sup>95</sup>. The acetone extracted oleoresin of curry leaves was evaluated for its antioxidant activity using a  $\beta$ -carotene/linoleic acid model system. It showed maximum activity of 83.2% at 100 mg/L. The methanol and water extracts showed activities of 16.7% and 11.3%, respectively, at the same concentration and volatile oil showed negligible (<10%) activity at 100 mg/L concentration. Mahanimbine and koenigine were identified for maximum antioxidant activity. Koenigine also showed a high degree of free radical-scavenging activity<sup>96</sup>. The ethanolic extract of *M. Koenigii* possessed potent antioxidant properties which were attributed to the presence of biologically active ingredients such as carbazole alkaloids, glycoside, triterpenoids and phenolic compounds<sup>97</sup>.

The status of enzymic (peroxidases, polyphenol oxidase) and non-enzymic antioxidants (ascorbic acid, reducing sugars, phenol and proteins) is estimated in both mature and tender leaves. Tender leaves were found rich in enzymic antioxidants as compared to mature leaves<sup>98</sup>. Antioxidant activity of various extracts of *M. koenigii* as measured by *in-vitro* nitric oxide scavenging activity follows the order seeds aqueous > leaf aqueous > leaf  $\text{CHCl}_2$ : MeOH > seed  $\text{CHCl}_2$ : MeOH<sup>99</sup>. Aqueous extract of *M. koenigii* leaves (10  $\mu\text{g/ml}$ ) inhibited 90 % of lipid peroxidation. It also inhibits the formation of diene, triene, tetraene conjugates in human erythrocyte membrane. Aqueous extract also inhibited 87 % of per oxidized lipid induced lysis at 300  $\mu\text{g/ml}$ <sup>100</sup>.

Adding fresh curry leaves in the diet of albino rat showed an alteration in peroxidation level to a beneficial extent<sup>101</sup>.

#### **Hypoglycemic activity:**

Feeding the leaves to rats produced hypoglycemia by increasing the hepatic glycogenesis as evident by increased activity of glycogen synthetase. A decrease in glycogenolysis and gluconeogenesis is reported and was evident from decreased activity of glycogen phosphorylase and gluconeogenic enzymes<sup>102</sup>.

A significant reduction in fasting blood sugar and postprandial blood sugar was observed by feeding (12 gm) leaves powder to Non Insulin Dependent Diabetes Mellitus patients (NIDDM)<sup>103,104</sup>. Aqueous and methanolic extracts of leaves and fruits of *M. koenigii* showed very good antidiabetic activity in alloxan-induced diabetic rats. Plasma insulin was observed with significantly high levels on the 43rd and 58th days of treatment in aqueous and methanol extracts of *M. koenigii* -treated groups<sup>105,106</sup>. Administration of mahanimbine at doses of 50 and 100 mg/kg intraperitoneally reduced fasting blood sugar, triglycerides, low-density lipoprotein, very low-density lipoprotein levels and increased high-density lipoprotein level were noted on<sup>107</sup>. Fruit juice decreased blood glucose level significantly at the 10th and 15th days of administration in alloxan-induced diabetic mice<sup>108</sup>.

Freeze dried leaves of *M. koenigii* lowered blood glucose level in normal and diabetic rats at oral administration of variable doses of 100, 200, 300 and 400 mg/kg. A fall of 41.5% in normal, 34.3% in sub-diabetic and 37.9% in mild-diabetic rats was observed with the dose of 300 mg/kg after 6 h of oral administration<sup>109</sup>.

Blood glucose level was reduced with the maximum fall of 14.68% in normal and 27.96% in mild diabetic animals when aqueous extract of leaves at a dose of 300 mg/kg was used<sup>110</sup>.

Intraperitoneally feeding of diet containing various doses of curry leaves (5%, 10% and 15%) to normal rats for 7 d as well as mild diabetic (blood glucose levels >175 mg/dL induced by alloxan 35 mg/kg intraperitoneally) and moderate diabetic rats (blood glucose levels >250 mg/dL induced by streptozotocin 60 mg/kg intraperitoneally) for 5 weeks showed varying hypoglycemic and antihyperglycemic effects<sup>111</sup>. The levels of glucose, glycosylated hemoglobin, insulin, thiobarbituric acid reactive substances (TBARS), enzymatic and non-enzymatic antioxidants were altered in diabetic rats, which reverted back to near control levels after treatment with extract of *M. koenigii*. These results suggested that *M. koenigii* treatment exerts a therapeutically protective effect in diabetes by decreasing oxidative stress and pancreatic  $\beta$ -cell damage<sup>112</sup>. All three extracts of dichloromethane, ethanolic and methanolic of *M. koenigii* leaves exhibited antilipase activity greater than 80%<sup>113</sup>.



Aqueous extract of leaves of *M. koenigii*, *Psidium guajava*, *Catharanthus roseus* at dose of 500 mg/kg body weight showed beneficial effects in various physiological or histological parameters altered during diabetic manifestations and these effects were found to be comparable to glibenclamide<sup>114</sup>. *M. koenigii* in combination with *Brassica juncea* showed their anti diabetic effect by increase in the concentration of hepatic glycogen and glycogenesis which was probably due to decreased activity of glycogen phosphorylase and gluconeogenic enzyme<sup>115</sup>. Streptozotocin-induced diabetic rats showed increases in blood glucose and glycosylated hemoglobin and a concomitant decrease in the levels of insulin and liver glycogen, increased activities of lactate dehydrogenase, glucose-6-phosphate, fructose-1, 6-diphosphatase and glycogen phosphorylase and decreased activities of hexokinase and pyruvate kinase (a glycogen synthase). These alterations were restored to near normal in the liver and kidney after treatment with ethanolic extract of *M. koenigii* leaves (200 mg/kg per day) for 30 d<sup>116</sup>. Mahanimbine when given orally (30 mg/kg per day) also significantly lowered the body weight gain as well as plasma TC and TG levels<sup>117</sup>. Aqueous and 50% methanol leaf extract-treated diabetic mice were found to lower TC, TG, and phospholipids than diabetic mice. Rising of glutathione and superoxide dismutase enzyme activities compared with diabetic mice showed antioxidant property of the extracts. Anti-inflammatory response was evident by interleukin-2, 4 and 10, and tumor necrosis factor- $\alpha$  expression. In addition, the reduction of apoptosis in pancreatic cells was found in the extract-treated diabetic mice<sup>118</sup>.

### Hepatoprotective activity

The protective nature of *M. koenigii* leaves extract was studied by Gupta et.al. The effect attributed to the combined effect of carbazole alkaloids – Mahanimbine, Girinimbine, Isomahanimbine, murrayazoline, Murrayazolidine, Mahanine and ascorbic acid,  $\alpha$ -tocopherol and mineral (Zn, Cu, Fe) contents of *M. koenigii* leaves extract. This study proved *M. Koenigii* a promising and a rich source of free radical quenchers, which have been mediated through hepatocyte membrane stabilizing activity alongwith the reduction of fat metabolism<sup>49</sup>. The normal morphology of cell was maintained after ethanolic challenge when aqueous extract containing tannins and carbazole alkaloids of *M. Koenigii* was given. Hepatoprotective activity was measured with respect to the different parameters studied and maintained normal morphology even after ethanolic challenge to the cells which was comparable to the protection offered by the standard drug L-ornithine-L-aspartate<sup>119</sup>. The acetone extract of dried bark powder showed prominent protection of liver cells as compared with the control group and other solvents in CCl<sub>4</sub>-induced liver damage<sup>120</sup>.

### Antimicrobial and anti-fungal activity:

Murrayanine, girinimbine and mahanimbine isolated from stem bark showed anti fungal activity against human pathogenic fungi<sup>61</sup>. 1- formyl-3 methoxy-6- methyl carbazole and 6,7-dimethoxy-1- hydroxy-3-methyl carbazole were reported to possess antibacterial and anti fungal property by Choudhury *et.al*<sup>37</sup>. Mahanimbine, murrayanol and mahanine from fresh leaves showed anti microbial and topoisomerase I and II inhibitory activity<sup>92</sup>. Marmesin- 1'-O- $\beta$ -D-galactopyranoside from stem bark showed anti bacterial, anti viral and anti fungal activity<sup>48</sup>. Essential oil was found to be effective against *Rhizoctania batiticola* (ED 50 0.112 %) and *Helminthosporium oryza* (0.1214%), and the effect is possibly due to presence of  $\beta$ -caryophyllene and gurjunene<sup>121</sup>. Essential oil and aqueous extract of leaf were found active against *Staphylococcus epidermidis*, *S. aureus* and streptococcus species. Crude extract and chloroform soluble fraction and petroleum ether soluble fraction showed a promising antibacterial activity against all the tested bacteria<sup>122-124</sup>. The crude extract of *M. koenigii* roots showed strong antibacterial activity<sup>64</sup>. Extract containing murrayanol and or isomahanine is used as microbicide in variety of industries due to high safety, strong activity, little odor and without coloring effect<sup>127</sup>.

### Pancreatic lipase inhibitory effect:

All three extracts (DCM, EtOAc and MeOH) of *Murraya koenigii* (L.) Spreng leaves (Rutaceae) exhibited antilipase activity greater than 80%. Bioactivity guided fractionation of the EtOAc extract led to the isolation of four alkaloids, namely mahanimbin, koenimbin, koenigicine and clausazoline-K, with IC<sub>50</sub>

values of 17.9 microM, 168.6 microM, 428.6 microM and <500 microM, respectively. This study reports for the first time the PL inhibitory potential of carbazole alkaloids from plants.<sup>130</sup>

### Effect on dental caries:

Feeding of murraya leaf extract in golden hamsters showed lower caries scores compared to control group<sup>128</sup>. Murraya extract or isomahanine, murrayanol and mahanine incorporated in foods (such as candies, biscuits, cakes, chewing gums, juices) showed 86.2% inhibition of methyl sulphhydryl formation by cultured *Fusobacterium nucleatum*<sup>126</sup>. *M. koenigii* leaf extract containing mahanin, isomahanin or murrayanol as active ingredient formulated in toothpaste, was found to be useful as oral disinfectant to protect against dental caries and periodontal disorders. They are also effective against *Streptococcus mutans* and *Porphyromonas gingivalis*<sup>126-129</sup>.

### Anticancer activity:

Koenoline isolated from root bark exhibited cytotoxic activity against the KB cell culture test system<sup>98</sup>. 9-formyl-3 methyl carbazole displayed weak cytotoxic activity against both mouse melanoma B 16 and adriamycin resistant P 388 mouse leukemia cell lines<sup>51</sup>. The effects of extracts of *M. koenigii* in in-vitro (short term incubation method and in-vivo (Dalton's ascitic lymphoma (DAL) anticancer models have been evaluated in male Swiss albino mice. DAL cells were injected intraperitoneally (106 cells) to the mice<sup>125</sup>. The anticarcinogenic potential of curry leaf using benzo (a) pyrene induced fore stomach and 7, 12 dimethyl benz (a) anthracene (DMBA) induced skin papillomas was studied. Chemo protective responses were measured as decrease in tumor burden (papillomas/mouse) and % of tumor bearing animals in both the models. Increase in level of acid soluble sulphhydryl compounds, glutathione S- transferase and DT-diaphorases were also measured. Antioxidant parameters (reduced glutathione, Super Oxide dismutase, catalases, glutathione peroxidase and glutathione reductase) were also elevated<sup>131</sup>.

The in-vitro anti-tumour promoting activity and antioxidant properties of Girinimbine isolated from the stem bark of *Murraya koenigii* was studied by Yih et.al. The *in vitro* anti-tumour promoting activity of girinimbine was determined by measuring the percentage inhibition of induced early antigen (EA) of EBV on the surface of Raji cells<sup>132</sup>

*M. koenigii* has been found to induce apoptosis in human myeloid cancer cell (HL-60). Results shows that mahanine down-regulates cell survival factors by activation of caspase-3 through mitochondrion-dependent pathway, and disrupts cell cycle progression<sup>133</sup>. Another study reported that mahanine, purified from the leaves of *M. koenigii*, has a dose- and time-dependent antiproliferative activity in acute lymphoid (MOLT-3) and chronic myeloid (K562) leukemic cell lines and in the primary cells of leukemic and myeloid patients, with minimal effect on normal immune cells including CD34 (+) cells<sup>134</sup>

### Anti-inflammatory activity

The alcohol extract of stem bark (1 gm/kg body weight) is effective against carrageenan-induced inflammation. Crude root extract also showed anti-inflammatory activity. Ethanolic extract of *M. koenigii* (EEMK) (300 and 400 mg/kg) showed antihistaminic actions in the histamine-aerosol protocol. The mast cell stabilization and antihistaminic effects of EEMK were suggested to be the probable mechanisms for its anti-inflammatory action<sup>135</sup>. The ethanolic extract (250 mg/kg) showed significant anti-inflammatory effects as compared with petroleum ether and chloroform extracts in acute carrageenan-induced paw edema method and yeast-induced hyperpyrexia method, respectively<sup>136</sup>

The methanol extract of leaves showed significant ( $P < 0.001$ ) reduction in carrageenan-induced paw edema in comparison with aqueous extracts. Petroleum ether and hexane extracts showed no reduction in paw edema<sup>137</sup> 9,12-octadecadienoic acid, a compound isolated from the methanolic extracts of leaves was reported to induce 85% reduction in paw edema at a dose of 150 µg/mL in reference to the standard anti-inflammatory drug aspirin which showed 68.62% reduction<sup>138</sup> The methanol extract showed significant ( $P < 0.001$ ) reduction in carrageenan-induced paw edema and analgesic activity evidenced by increase in the reaction time by Eddy's hot plate method and percentage increase in pain in formalin test<sup>139</sup>

### Immunomodulatory activity

The methanolic extract of *M. koenigii* showed significant increase in phagocytic index by rapid removal of carbon particles from blood stream. The extract also increased the antibody titre against ovalbumin and protection towards cyclophosphamide-induced myelosuppression in albino mice<sup>137</sup>. Oral administration of the aqueous extract of leaves at doses of 250 and 500 mg/kg significantly enhanced the delayed-type hypersensitivity reaction induced by ovalbumin. The extract also potentiated the production of circulating antibody titre significantly in response to ovalbumin<sup>141</sup>.

#### **Effect on bronchial disorders:**

Herbal composition containing organic extract of any plant part of *Murraya* (leaves, bark, roots and seeds) is useful in the treatment and remedy of bronchial respiratory troubles by blocking 5-lipoxygenase activity<sup>128</sup>.

#### **Cardioprotective activity**

The studies indicated that the aqueous extract of Curry leaf protects the rat cardiac tissue against cadmium-induced oxidative stress possibly through its antioxidant activity.

Treatment of rats with cadmium also caused alterations in the activities of mitochondrial Krebs's cycle as well as respiratory chain enzymes. All these changes were ameliorated when the rats were pre-treated with an aqueous extract of Curryleaf (*Murraya koenigii*).<sup>142</sup>

#### **Antiosteoporotic activity**

A new carbazole alkaloid 8,8'-biskoeningine was a symmetrical dimer of the carbazole alkaloid koeningine and showed antiosteoporotic activity in the cathepsin B model with IC<sub>50</sub> of 1.3 µg/mL<sup>143</sup>.

#### **Alzheimer disease therapy**

Administration ethanolic extract of *M. Koenigii* Leaves for 15 d produces significant dose-dependent improvement of memory. The results also indicated to reduce the brain cholinesterase activity and total cholesterol level<sup>121</sup>. Diet rich in *M. koenigii* leaves produced significant dose-dependent improvement in the memory scores of young and aged mice and significantly reduced the amnesia induced by scopolamine (0.4 mg/kg, intraperitoneally) and diazepam (1 mg/kg, intraperitoneally). Also, brain cholinesterase activity and total cholesterol levels were reduced by the MKL diets. Acetylcholinesterase inhibitory potential of a carbazole alkaloid, mahanimbine, from *Murraya koenigii* leaves was studied by Kumar et.al. This study is the first to reveal this activity in carbazole alkaloid mahanimbine, isolated from *Murraya koenigii*<sup>144</sup>. The effect of total alkaloidal extract from *M. koenigii* leaves (MKA) on cognitive functions and brain cholinesterase activity in mice were determined. In vitro β-secretase 1 (BACE1) inhibitory activity was also evaluated. The brain cholinesterase activity was also reduced significantly by total alkaloidal extract of *M. koenigii* leaves. The IC<sub>50</sub> value of MKA against BACE1 was 1.7 µg/mL. The study indicates MKA to be a useful remedy in the management of Alzheimer's disease and dementia<sup>145</sup>.

#### **antiobesity and antihyperlipidemic activities**

The dichloromethane (MKD) and ethyl acetate (MKE) extracts of *Murraya koenigii* leaves significantly reduced the body weight gain, plasma total cholesterol (TC) and triglyceride (TG) levels significantly. The observed antiobesity and antihyperlipidemic activities of these extract are correlated with the carbazole alkaloids, Mahanimbine. When it was given orally (30 mg/kg/day) significantly lowered the body weight gain as well as plasma TC and TG levels. These findings demonstrate the excellent pharmacological potential of mahanimbine to prevent obesity<sup>146</sup>.

#### **Antiamnesic and wound-healing activity**

Antiamnesic potential of *Murraya koenigii* leaves was also studied<sup>147</sup>. Aqueous extract of *M. koenigii* accelerates the wound-healing process by decreasing the surface area of the wound. Aqueous extract of leaves showed marked reduction in wound area in comparison with the control group from 4th day onwards in albino rats by excision wound model<sup>148</sup>.

#### **Kidney protective activity**

Aqueous extract of leaves produced a significant dose-dependant decrease in serum urea and creatinine levels ( $P < 0.001$ ), and a marked increase in the levels of plasma antioxidant capacity ( $P < 0.01$ ) in diabetic rats, compared with the control (non-diabetic) subjects. Histological studies of the kidneys of these animals showed comparable tissue regeneration by the aqueous extract<sup>149</sup>

### **Antipyretic activity**

The ethanolic extract of leaves of *M. koenigii* was investigated for antipyretic activity in rats using yeast-induced pyrexia model. Ethanolic extract at a single dose of 300 mg/kg produced significant antipyretic activity ( $P < 0.01$ ) in albino rats as compared with the standard drug paracetamol<sup>150</sup>.

### **histopathological activity**

When whole curry leaves with mustard was given to rat at normal human intake, it did not show any histopathological changes. It did not cause any adverse effect on food efficiency ratio, red blood cell count, white blood cells, total count, differential counts or on the levels of blood constituents, like serum electrolytes, blood urea, haemoglobin, total serum protein, albumin-globulin ratio, fibrin level, glycosylated haemoglobin and the activity of aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase in serum<sup>151</sup>

### **Radiation protection activity**

The effect of 4 Gy gamma radiation 30 min after the last injection of 100 mg/kg of methanolic extract of *M. koenigii* for 5 consecutive days was observed on adult Swiss albino mice. The extract itself increased the glutathione and enzymes levels, whereas radiation significantly reduced all values. Pretreatment with the extract reduced lipid peroxidation rate induced by radiation. The result demonstrated that *M. koenigii* leaves possess good antioxidant activity in vitro and are able to protect against radiation-induced depletion in cellular antioxidants<sup>152</sup>. The methanolic extract showed protection against gamma radiation and cyclophosphamide-induced chromosomal damage in Swiss albino mice at a single dose of 100 mg/kg body weight<sup>153</sup>.

### **Anti ulcer activity**

Anti ulcer activity was observed using aqueous extract at doses of 200 and 400 mg/kg. It produced significant inhibition of gastric lesion induced by non-steroidal anti-inflammatory drugs and pylorus ligation-induced ulcer. The extract reduced ulcerative lesion, gastric volume and free and total acidity but raised the pH value of gastric juice in pylorus ligation model. The results obtained suggested that the extract possesses significant antiulcer activity<sup>154</sup>.

### **Antitrichomonal activity**

Carbazole alkaloids and their derivatives from *M. koenigii* leaves showed antitrichomonal activity against *Trichomonas gallinae*. Girinimbine and girinimbilol with IC<sub>50</sub> values of 1.08 and 1.20 mg/mL were the most active. Acetylation of girinimbilol and mahanimbilol improved their activities to 0.60 and 1.08 mg/mL<sup>155</sup>

### **Antidiarrhoeal activity**

Two bioactive carbazole alkaloids, namely, kurryam and koenimbine obtained from fractionated n-hexane extract of the seeds of *M. koenigii* exhibited significant inhibitory activity against castor oil-induced diarrhoea and prostaglandin E<sub>2</sub>-induced enteropooling in rats. These compounds also produced a significant reduction in gastrointestinal motility in the charcoal meal test in Wistar rats<sup>27</sup>

Das *et.al* has reported mahanimbine toxicity against the larvae of *Culex quinquefasciatus*<sup>157</sup>

### **Anthelmintic activity**

Ethanolic and aqueous extracts from *M. koenigii* leaves were investigated for their anthelmintic activity against *Pheretima posthuma*. Both the extracts exhibited significant anthelmintic activity at concentration of 100 mg/mL<sup>158</sup>. The alcoholic extract produced more significant anthelmintic activity than petroleum ether extract<sup>159</sup>

**Cosmetic use**

Hyaluronidase inhibitors are extracted from *M. koenigii* and are formulated in a cream base by Tsuneo et.al. *M. koenigii* extract is included in a skin-lightening cosmetic for its moisturizing, antioxidant and hyaluronidase inhibitory activity. Herbal composition containing *M. koenigii* stem extract as one of the ingredients showed skin lightening and rough skin improving effect<sup>156</sup>. *M. koenigii* was studied for sun protection. On the basis of this study it was suggested that it can be used to maintain the natural pigmentation of the skin or can be used as an adjuvant in other formulations to enhance the activity. Curry leaf oil cream showed the low sun protection factor (2.04±0.02), so the cream can be used in maintaining the natural skin pigmentation or it can be used as additives in other formulations to enhance the activity<sup>160</sup>.

**Table: 1 List of Active compounds of *Murraya Koenigii* and its biological activities**

<i>Murraya koenigii</i> compounds	Source	Biological activity	Reference
Lutein	Leaves	Antioxidant activity	34
Tocopherol	Leaves	Antioxidant activity	34
	Leaves	Hepatoprotective	49
Carotene	Leaves	Antioxidant activity	32
Koenimbine	Leaves	Antioxidant activity	34
O-methyl murrayamine A	Leaves	Antioxidant activity	35
O- methyl mahanine	Leaves	Antioxidant activity	35
Isomahanine	Leaves	Antioxidant activity	35
	Leaves	Anti caries	126
Bismahanine	Leaves	Antioxidant activity	35
Bispyrafoline	Leaves	Antioxidant activity	35
Euchrestine	Leaves	Antioxidant activity	36
Bismurrayafoline E	Leaves	Antioxidant activity	36
Mahanine	Leaves	Antioxidant activity	36
	Leaves	Anti caries	126
	Leaves	Hepatoprotective	49
	Stem and bark	Antimicrobial	92
		Topoisomerase I and II inhibitory activity	92
1- formyl 3-methoxy-6- methyl carbazole	Leaves	Hepatoprotective	49
	Leaves	Anti bacterial and anti-fungal activity	12
6,7-dimethoxy-1-hydroxy-3-methyl carbazole	Leaves	Anti bacterial and anti-fungal activity	29
Mahanimbine	Leaves	Mosquitocidal	157
	Stem and bark	Antimicrobial	61
	Leaves	Hepatoprotective	49
		Anti microbial	62
		Topoisomerase I and II inhibitory activity	62
		Antioxidant activity	62
		Antioxidant activity	30
		Toxicity on <i>Culex quinquefasciatus</i> larvae	42
Stem bark	Anti fungal	33	
Isomahanimbine	Leaves	Hepatoprotective	49
Murrayanol	Leaves	Mosquitocidal	157
	Leaves	Anti-microbial	62

<i>Murraya koenigii</i> compounds	Source	Biological activity	Reference
		Topoisomerase I and II inhibitory activity	62
	Leaves	Anti inflammatory	62
		Anti caries	124
Marmesin-1'-O-beta-D-galactopyranoside	Stem bark	Anti viral	48
		Anti bacterial	48
		Anti fungal	48
Gurjunene	Leaves	Anti microbial	120
Murrayanine	Stem bark	Anti fungal	48
	Stem and bark	Antimicrobial	61
Girinimbine	Stem bark	Anti fungal and antibacterial	48
	Stem bark	Anti-cancer	132
	Leaves	Hepatoprotective	49
Murrayazoline	Leaves	Hepatoprotective	49
Murrayazolidine	Leaves	Hepatoprotective	49

## CONCLUSION

Keeping in view the tremendous pharmacological activities and wealth of literature available, *M. koenigii* may be utilized to alleviate the symptoms of variety of diseases as evident from the pre-clinical data.

Although crude extract from various parts of curry neem have numerous medical applications, modern drugs can be developed after extensive investigation of its bioactivity, mechanism of action, pharmacotherapeutics, toxicity and after proper standardization and clinical trials.

The available literature and wide spread availability of *M. koenigii* in India thus makes it an attractive candidate for further pre-clinical and clinical research.

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