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THE SIGNIFICANCE OF MURRAYAKOENIGII (L.) SPRENG LEAVES: A MINI-REVIEW

Azad, A.K.[1*]; Babar, Z.M.[1]; Wan Mohd Azizi W.S.[1]; Sunzida, N.K.[2]

[1]Department of Basic Medical Sciences, Faculty of Pharmacy, International Islamic University Malaysia, 25200 Kuantan, Pahang, Malaysia.
[2]Gonoshasthaya SamajVittik Medical College, Gono University, Dhaka, Bangladesh.

[*]azad2011iium@gmail.com

Abstract

This current review is precisely aimed to focus the traditional uses and the significance of *Murrayakoenigii* (L.) Spreng leaves in preventing CNS disorders. This review was done based on the scientific literature, traditional uses and herbal treatment which were collected from the existence database, google scholar, pubmed, science direct and scopus. Based on this review, *Murrayakoenigii* (L.) Spreng leaves has strong effect on CNS disorder, antioxidant activity, neuroprotective effects, anti-inflammatory and analgesic property etc. However, scientist should give more concentrate with this plant leaves due to the presence of its high concentrate of different phytochemical groups. Therefore, It could be the main source of crude medicine for future generation to solve the current issue like CNS disorders, cancer and HIVs. This current reviewed, recommended looking more effective bioactive compounds and its potential preclinical trial.

Key words: *murrayakoenigii*, antioxidant, CNS, anti-inflammatory, analgesic, bioactive compound.

Introduction

Traditional medicine is the core of modern medicine [1-4]. From an ancient era to till, people are frequently using natural remedies for each and every diseases while they are facing old or new health problem or other illness [5-8]. *Murray koenigii* (L.)Spreng., is a member of *Rutaceae* family known as '*Curry leaves' or 'Meethineem'*native to India has been proved to show diverse biological activities against neurodegeneration. It is an aromatic, more or less deciduous shrub or a small tree having a maximum height of up to 6 m with a trunk up to 40 cm in diameter. Its family represents more than 50 genera and 1600 species [9]. It is abundantly found in India, Bangladesh, Philippines, Malaysia and Andaman Islands. The most well-known species of them in Malaysia are *M. paniculata* and *M. koenigii* for their wide range of uses as flavouring agent in curries [10].

India has cultivated in large numbers for its vast uses in herbal medicines and dishes as spice. The presence of some vitamins, carbazole alkaloids, terpenoids, phenolic compounds and mineral content such as calcium, iron, zinc and vanadium in *M.koenigii* have been discovered by phytochemical studies. The leaves of *M.koenigii* have been widely used as condiments for centuries. Few of the recent studies have proved that the leaves of *M.koenigii*(L.) Sprenghave memory and learning enhancing effects which in turn exhibited neuroprotection activities [11] Traditionally, it has been used as antiemetic, antidiarrhoreal, dysentery, febrifuge, blood purifier, tonic, stomachic, flavouring agent in curries and pickles. Its oil is being used topically for curing bruises and cuts, in soap and perfume manufacturing.

Other several biological activities of *M. koenigii* leaves have been reportedfor its anti-hypercholesterolemic, anti-microbial, efficacy against colon carcinogenesis, anti-oxidant, anti-diabetic, anti-hypertensive, cytotoxic effects and in the treatment of respiratory tract difficulties [8, 11-25]. The leaves are extensively used in almost every dish of Malaysia for its flavouring and delicious taste properties [26].This current review is precisely aimed to focus mainly on its antiamnesic effects of the leaves which have been introduced recently [27]. Phytochemistry of *Murrayakoenigii* (L.)Sprengleaves (Table 1-3)

Methods

Data were collected from several very well reputed scientific data base google scholar, pubmed, science direct and scopus.

Results

Pharmacological Properties

Antioxidant activity

The content of total anti-oxidant activity of *M.koenigii* leaves was found highest (2691µmol of Ascorbic acid/ gm) amongst all green leafy vegetables [36]. A recent study has suggested thatM.koengii leaves have significantly protected cardiac tissue of rats against cadmium-induced oxidative stress which was supposed to be due to its anti-oxidant property [37]. It was also found that the methylene chloride (CH2Cl2) extract and the ethyl acetate (EtOAc) soluble fraction of the 70% acetone extract of M. koenigii leaves prolonged the Oil Stability Index (OSI) values significantly as compared to those of α-tocopherol and BHT [15, 16]. The significant anti-oxidant activity of M.koenigii leaves was thought to be because of its active carbazole alkaloids which are active against oxidation (e.g. mahanine, mahanimbicine) [15]. The overall review showed that the leaves of M. koenigii might be a potent and novel therapeutic agent for free radical scavenging in cancer patients and those who have been suffering from cadmium oxidative stress occupationally [37].

Neuroprotective effects of M.koenigii leaves

Another study with total alkaloidal extracts of *M .koenigii* leaves in doses of 20 and 40 mg/kg p.o. found increased values of protective antioxidants like glutathione peroxidase (GPX), reduced glutathione (GSH), glutathione reductase (GRD), Superoxide dismutase (SOD) and catalase (CAT) in brain homogenate [5, 27]. It also demonstrated that M.koenigii leaves extract could reduce lipid peroxidation (LPO) and nitric oxide (NO) that produces an oxidation product called peroxynitrite. The previous study also found that there was an increase in the acetylcholine (Ach) levels and decrease in the anticholinesterase (AchE) activity [5, 20]. Besides reducing brain cholinesterase activity, *M.koenigii* extracts significantly improved cognitive functions as evidenced by the significant increase in the memory scores of young and aged mice while the extracts reserved the amnesia induced by scopolamine (0.4 mg/kg i.p.) and diazepam (1 gm/kg i.p.).It was also proved that ethanolic extract of *M.koenigii* resulted in increase in grip strength of STZ-induced diabetic rats which developed neuropathy at 9thsingle injection. Thus, M.koenigii leaves extracts can be supplemented in the management of Alzheimer's disease and dementia or other neurodegenerative diseases [5].

A very recent study conducted by (Patil R. et al.,

2012) has suggested that *M.koenigii* leaves may have great potential against neuroleptic-induced orofacial dyskinesia because it has observed the significant level of restoration of protective anti-oxidant enzymes*i.e.,* SOD, CAT, GSH and inhibited LPO in the forebrain region when compared with reserpine-induced animals having orofacial dyskinesia. This study has also investigated that methanolic extract of *M.koenigii* leaves (MEMKL)inhibited haloperidol-induced catalepsy. It has concluded that MEMKL treatments on reserpine and haloperidol-induced animals (Swiss Albino male mice 22-25 gm and Wistar Albino male rats 150-200 gm) showed significant inhibition of vacuous chewing movement (VCM), tongue protrusion (PT), orofacial burst (OB) and catalepsy in the said animals [38].

Anti-inflammatory and analgesic property of M.koenigii leaves

It has been recommended by few studies that administration of *M.konigii* leaves extracts (MKLE) of petroleum ether and its separated alkaloids in a dose dependent manner (100 mg and 300 mg/kg p.o) could significantly decrease the number of acetic acid-induced writhing while rise the latency of paw licking in hot plate method (HPM) and basal reaction time in tail immersion method (TIM). It was also suggested that chronic administration of MKLE (more than 15 days or two weeks) might have significant analgesic effect [39]. The study also proved that administration of methanolic extract of the dried leaves of M.koenigii at doses of 100, 200 and 400 mg/kg body weight to Albino rats could significantly ($P<0.001$) reduce the carrageenan-induced paw edeme.In that study,theanalgesic activity of M.koenigii leaves was proved by an increase in the reaction time by Eddy's hot plate method and formalin-induced paw licking method, which was found statistically significant ($P<0.05$). It has concluded that the anti-inflammatory and analgesic effects of M.koenigii leaves were comparable to standard drug Diclofenac(10 mg/kg, p.o) [40].

Carbazole Alkaloids of M.koenigii(L.)Spreng: The Potent Bioactive in Phytotherapy Research

According to some of previous studies carried by [2, 9, 15, 19, 21, 26, 41-42], M.koenigii is a very well-known natural source rich in carbazole alkaloids that possess many potent biological activities even in crude extracts level. It has been reported that the plants of Rutaceousfamilyand genus Murrayacontained various bioactive constituentswhich could effectively be used against tumours, oxidative stress, mutagen, inflammation, flu, diarrhoea, viral infections [43], hypertension, diabetes mellitus, diabetes-induced renal damage [44], bacterial infections, fungi, dysentery, emesis, stomach pain, hyperthermia,Alzheimer's disease and dementia [7, 15, 19, 27, 45-50].

Few recent studies [29, 34, 51] have reported that three carbazole alkaloids namely mahanine,pyrayafoline-D and murrafoline-Ifrom *M.koenigii*leaves extract of acetone showed relatively significant cytotoxic effect against human leukemic cells (HL-60) in a time-dependent manner on percentage of apoptotic cells with fragmented nuclei and condensed chromatin when examined each of the alkaloid under fluorescence microscope with Hoechst 33342 staining protocol. These studies have also suggested that the three alkaloids potentially induced apoptosis in HL-60 cells through dysfunction of mitochondria by activation of the CASP9 and CASP3 genes. Some of the isolated carbazole alkaloids commonly found in *M.koenigii* leaves are koenine, koenimbine, koenigine, koenidine, mahanimbine, mahanine, pyrayafoline-D, euchrestine-B, murrafoline-I and mahabinine-A in which murrafoline-I and mahnimbine-A are newly discovered binary carbazole alkaloids. Other new binary carbazole alkaloids found in *M.koenigii* leaves and root barks are 8, 8''-biskoenigine and its monomer koenigine, girinimbine, isomahanimbine and koenimbidineb [52, 53].It has been claimed that giriminbine (3,3,5-trimethyl-11H-pyrano[3,2-a]carbazole) which first isolated compound was pyranocarbazole from the stem barks of M. koenigii [54] has shown the inhibition of growth and induced apoptosis in human hepatocellular carcinoma (HepG2) cells when examined the morphological features of apoptosis by normal inverted microscope and, DNA fragmentation and elevated levels of CASP3 in HepG2 cells by Hoechst 33342 assay while MTT and LDH assays showed decreased cell viability and cytotoxicity in a dose-and time-dependent manner [55].

Acute Toxicity (in-vivo&in-vitro) studies of M.koenigii (L.) Spreng leaves

The current review on acute toxicity studies of *M.koenigii* (L.) Sprengleaves aimed to bring a glance of light on different types of solvents, doses, dose frequencies, duration of treatments, results, and methods used by previous researchers for different activities of carbazole alkaloids and essential oils of *M.koenigii*leaves.This review would help the future researchers to choose an effective method with

suitable solvent, extract, dose, duration etc. (Table-4)

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Table1: The list of isolated phytoconsitiuentsof *M.koenigii* leaves

Sl.	Phytoconstituent	Solvent	Reference
01	Mahanine	Methanol	[28-29]
02	Koenine	Methanol	[30]
03	Koenigine	Methanol	[30]
04	Koenidine	Methanol	[15]
05	Girinimbiol	Methanol	[30]
06	Girinimibine	Methanol	[30]
07	Koenimbine	Methanol	
08	O-methyl murrayamine A	Methanol	
09	O-methyl mahanine	Methanol	
10	Iso-mahanine	Methanol	
11	Bismahanine	Methanol	
12	Bispyrayafoline	Methanol	[16]
13	Scopotin		
14	Murrayanine		[31]
15	Calcium		
16	Phosphorus		
17	Iron		
18	Thiamine		
19	Riboflavin		
20	Niacin		
21	Vitamin C		
22	Carotene		
23	Oxalic acid		

Table 2: The list of phytoconstituents of essential oil from*Murrayakoenigii* (L.)Spreng. Leaves;

Sl.	Phytoconstituents	Solvent	Reference
01	α-phellandrene	Et.OH	[32]
02	D-sabinene	Et.OH	[32]
03	D-α-pinene	Et.OH	[32]
04	Dipentene	Et.OH	[32]
05	D-α-terpinol	Et.OH	[32]
06	Caryophyllene	Et.OH	[32]
07	5,8-Dimethylfuranocoumarine	Pet.ether&Et.OH	[33]
08	1-al,3 [6',6'-dimethyl-5-hexane] carbazole	Pet.ether&Et.OH	[33]
09	β-sitosterol	Pet.ether&Et.OH	[33]

Table 3: Compounds found in the essential oil of *M. koenigii* (L.)Spreng leaves by GC-MS method

Sl.	Name of compounds	Amount (%)
01	α-thujene	1.47
02	α-phellandrene	0.07
03	α-terpinene	2.39
04	α-caryophyllene	2.81
05	α-cadinol	0.08
06	β-phellandrene	0.07
07	β-elemene	1.92
08	β-myrcene	3.20
09	γ-terpinene	2.70
10	γ-elemene	1.96
11	δ-cadinene	0.10
12	δ-elemene	0.04
13	Allyl(methoxy)dimethylsilane	2.58
14	Camphene	0.09
15	Caryophyllene	9.49
16	Caryophyllene oxide	1.02
17	Cis-sabinenehydrate	1.46
18	Cis-piperitol	0.13
19	Cubenol	0.08
20	1-chloroheptacosane	0.06
21	3-carene	54.22
22	3-phenylbutyrophenone	1.15
23	4-terpineol	2.80
24	Eucalyptol	0.11
25	Eudesma-4(14),11-diene	0.18
26	(E)-ocimene	0.23
27	Isobornyl acetate	0.07
28	Juniper camphor	0.45
29	Limonene	0.84
30	Linalool	0.19
31	m-cymene	0.30
32	Naphthalene	0.09
33	Nerolidyl acetate	0.15
34	Neryl propionate	0.04
35	12-oxabicyclo[9.1.0]dodeca-3,7-diene,1,5,5,8-tetramethyl	0.07
36	1,4-methanoazulen-9-ol, decahydro-1,5,5,8a-tetramethyl	0.06
37	2(1H)-naphthalenone,4a,5,6,7,8,8a-hexahydro-4a,8a-dimethyl	0.05
38	Phytol	0.93

Table-4: **In-vivo and In-vitro Model with different dose & different solvents extract.**

In-vivo Model	Duration	Dose (mg/kgb.w)	In-vitro Model	Dose	Solvent	Ref	Result
a.SD male rats	33 Days[a.] N/A[b.]	5000, 600, 200 &400[a.]	**b**.*(210PJTU), (SR16677-PRSP), (SR1-TU),(N123 JTU), (ATCC 25619); MFC-7 & P388 cell lines*	25.0-175.0 (MIC) for 100.0-500.0 µg/ml (MBC)[b.]	Water[a.] Mahanine, mahanimbicine, Mahanimbine & essential oil of Ethanol[b.]	[44][a.] [56][b.]	Non-toxic[a.] Antibacterial &cytotoxic[b.]
c.Male Wistar Rats	15 Days[c] N/A[d.]	300 & 600[c.]	**d**. Human Leukemia cell line (HL-60)	30µM of isolaetedmahanine, pyrayafoline-D &murrafoline-I[d.]	Ethanol[c.] Acetone[d.]	[57][c.] [47][d.]	Non-toxic[c.] Cytotoxic[d.]
e.Isolated Frog heart (either sex)	15 min[e], 24 h & 48 h[f.]	65.0-1000.0µg[e.]	**f.***Bacillus subtilis,E.coli, S.aureus,S.typhi, Aspergillusniger, C.albicans&T.rubrum*	1000µg/ml[f.]	Ethanol[e.] Hexane,methanol, chloroform &water[f.]	[58][e.] [25][f.]	Positive inotropic effects[e.,] Antimicrobial &antifungal[f.]
g.Animals	N/A[h.] 12 Days[g.]	Once a day[g.]	**h.** Egg cells	25,50,75 & 100%[h.]	Acetone[h.] N/A[g.]	[59][h.] [22][g.]	Ovicidal[h.] Stopbleeding[g.]
i. SD female rats	18 Days[i.] N/A[j.]	(19.25%, 12.60%, 88.54% & 91.78%)[i.]	**j.**Hep G2 Cell line[j.]	100µg/ml & 500µg of WE, CA &T.[j.]	Ethanol &Water[i.], Water[j.]	[60][i.] [61][j.]	Wound healing[i.] Hepatoprotective[j.]
k.STZ-induced severe diabetic rats & HFD-induced obese rats	30Days & 14 Days[k.] 14 Days[l.]	300mg/kg[k.]	**l.***Trichomonasgallinae*	1.08 &1.20 µg/mli.e,. (IC_{50})**l.**	Water & Dichloromethane & ethylacetate[k.,] MethanolicGirinimbine&girinimbilol[l.]	[62-63][k.] [30]**l.**	Lipid lowering, anti-diabetic &antiobesityeffects[k] . Anti-trichomonal effect [l.]
m. CCl_4-induced hepatotoxi-c rats	N/A[m.] 30min & 180 min[n.]	200, 400 & 600mg/kg[m.]	**n.***Listeria innocua*	300, 400 & 600 µg/ml (MIC)[n.]	Hydroethanolic[m.] SFME & HD oil[n.]	[64-67][m.] [65][n.]	Hepatoprotectivepotential[m.] Antibacterial[n.]
			p.*A.egypti*	250ppm-900ppm[p.]	Acetone &Pet.ether[p.]	[68-74][p.]	Larvicidal[p.]