ANTI-TRICHOMONAL ACTIVITIES OF EXTRACTS AND FUROCOUMARINS OF *MURRAYA KOENIGII* FRUITS

A.C. ADEBAJO[1,+], K.A. OLANIYAN[2] and C.O. ADEWUNMI[2]

1. Department of Pharmacognosy, Obafemi Awolowo University, Ile-Ife, Nigeria.
2. Drug Research and Development Unit, Obafemi Awolowo University, Ile-Ife, Nigeria.

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Abstract

Murraya koenigii has been used in ethnomedicine for its anti-infective and anti-protozoal properties and therefore the methanolic extracts of pericarps and seeds and the furocoumarins isolated from the seeds were evaluated for anti-trichomonal activities using *Trichomonas gallinae*. The demonstrated anti-trichomonal activities of the fruit extracts and isolates that were comparable to that of Metronidazole, the standard anti-trichomonal agent used, show that furocoumarins acting synergistically were the active constituents of this furocoumarin-producing *M. koenigii*. The structure activity relationships of the furocoumarins showed that a free H-8 may be important for this activity as prenyl substitution at C-5 gave a better activity than at C-8. The presence of double bond(s) in the substituents gave poorer activity while those of oxygenated groups such as epoxy, hydroxyl and another lactone significantly increased the activity. The low toxicity profile of the extracts using haemagglutination activity of formaldehyde fixed bovine erythrocytes supports the internal use of the plant in medicine. Hence, use of this plant as a spice similar to the carbazole-producing *M. koenigii* would confer on the user additional protection against trichomonads and may confirm the ethnomedicinal uses of the plants in the treatment of protozoal diseases such as amoebiasis, dysentery and trichomoniasis as well as represent a cheaper alternative to metronidazole.

Key words: Anti-trichomonal activities, toxicity, *Trichomonas gallinae*, furocoumarins, *Murraya koenigii*.

1. Introduction

Murraya koenigii (L.) Sprengor is a spicy rutaceous medicinal plant grown mostly in the tropics and subtropics for the medicinal and flavourant properties of the leaves and fruits (Dastur, 1970; Gupta and: Nigam, 1971; Stone, 1985). Native to Indo-China, it is commonly called Curry leaf Tree and used in most homes of the world to spice foods (Chakraborty *et al.*, 1965; Adebajo, 1997). Volatile oils (Dutt, 1958; Nigam and Purohit, 1961; Macleod and Pieris, 1982; Wong and Tie, 1993, Onayade and Adebajo, 2000; Rana *et al.*, 2004), mono- and dimeric carbazole alkaloids (Fiebig *et al.*, 1985; Atta-ur-Rahman *et al.*, 1988; Hegnauer, 1990; Chakraborty and Roy, 1991; Ito *et al.*, 1993; Reisch *et al.*, 1992, 1994a; Bhattacharyya *et al.*, 1994; Adebajo, 1997; Chakrabarty *et al.*, 1997; Nutan *et al.*, 1998), simple furo- and pyrano-coumarins (Gupta and Nigam, 1971; Bhattacharyya and Chakraborty, 1984; Reisch *et al.*, 1994b, c; Adebajo, 1997; Adebajo *et al.*, 1997; Adebajo and Reisch, 2000) have been the major constituents reported from the plant's parts. Since it is an ancient Indian medicinal plant, its leaves have been ethnomedicinally used as tonic, febrifuge, stomachic and anti-vomiting. The leaf, stem and root are used externally in skin eruptions and bites of venomous animals while the bark and root are used as stimulant. Other uses are as carminative, hypotensive, hypoglycaemic, anti-periodic and anti-fungal (Chakraborty *et al.*, 1965; Das *et al.*, 1965; Dastur, 1970; Gupta and Nigam, 1971; Nutan *et al.*, 1998). It is also eaten raw for curing dysentery and diarrhoea (Dastur, 1970; Gupta and Nigam, 1971; Rana *et al.*, 2004), uses probably confirmed by its anti-amoebic property and activity against *Entamoeba histolytica* (Bhakuni *et al.*, 1969; Kapil, 1971; Kong *et al.*, 1986). Pharmacologically and biologically, antimicrobial (Nutan *et al.*, 1998), antitumuor (Fiebig et al. 1985; Chakrabarty *et al.*, 1997), α-amylase inhibitory (Bawden *et al.*, 2002), anti-oxidative (Tachibana *et al.*, 2001), cytotoxic, depressant, anti-trichomonal (Nutan *et al.*, 1998; Adebajo *et al.*, 2004, 2006), anti-hypertensive, -treponemal, -spasmodic (Bhakuni *et al.*, 1969; Kapil, 1971; Kong *et al.*, 1986; Adebajo, 1997) and anti-diabetic (Naraya and Sastry, 1975; Adebajo *et al.*, 2006) activities for the extracts while antioxidative (Khan *et al.*, 1997), hypoglycaemic (Iyer and Mani, 1990; Khan *et al.*, 1995 a, b; Yadav *et al.*, 2002; Grover *et al.*, 2003), hypocholesteromeia (Khan *et al.*, 1996 a, b) properties for the powdered leaf have been reported. Furthermore, anti-oxidant, -tumour, -microbial, -inflammatory, trypanocidal and

+ *corresponding author* (email: caadebajo@oauife.edu.ng)

mosquitocidal activities have been indicated for some of these alkaloids isolated from the plant and other sources (Das *et al.*, 1965; Fiebig *et al.*, 1985; Chakrabarty *et al.*, 1997; Nutan *et al.*, 1998; Ramsewak *et al.*, 1999; Itoigawa *et al.*, 2000; Nakatani, 2000; Adewunmi *et al.*, 2001). There has been no pharmacological report on furocoumarins isolated from the plant, however, activities such as the treatment of skin lesions e.g. vitiligo, feeding repellent protection against polyphageous insect larvae, inhibition to crown gall tumours and some enzymes, inhibition of the synthesis of albumins and proteins, especially of nucleic acids, anti-tumour, antimicrobial and toxic effects to some animals, have generally been reported for furocoumarins (Murray *et al.*, 1982).

Trichomonas vaginalis and *T. gallinae* cause trichomoniasis in man and animals with terrible medical implications and Metronidazole is the drug of choice. *Trichomonas gallinarum* affects birds including poultry, causing high morbidity and mortality especially in young birds. The observations that *T. vaginalis* is becoming resistant to metronidazole in about 5% of the population (Munoz *et al.*, 1998) coupled with the fact that metronidazole has unpleasant adverse effects (Narcisi and Secor, 1996) have led to search for phytochemicals in African medicinal plants with potential antitrichomonal activities (Omisore *et al.*, 2005). The furocoumarin-producing plant of *M. koenigii* has been reported as a geographical race of the carbazole-producing Curry leaf (Reisch *et al.*, 1994 a, b; Adebajo and Reisch, 2000). Since the extract of the carbazole- producing plant and its carbazole constituents has been shown to have anti-trichomonal activity (Adebajo *et al.*, 2004, 2006), we therefore investigated the furocoumarin-producing plant and its isolated furocoumarins for the same activity, using *T. gallinae*. Furthermore, since the leaf and fruit are freely eaten, the abundant pharmacological reports on *M. koenigii* and the report of moderately toxicity for the carbazole producing plant (Adebajo *et al.*, 2006), it became important to evaluate the potential toxicities of the two *M. koenigii* plants by determining the agglutination and haemagglutination values of their methanol extracts.

2. Materials and Methods

Plants Material, Extraction and Isolation:

The authentication, collection, extraction and isolation of the constituents of *Murraya koenigii* fruits were as previously reported (Adebajo *et al.*, 1994a,b, 1997; Adebajo and Reisch, 2000). The dried fruits were dehulled and the pericarps separated from the seeds. Fresh cold MeOH extracts of the seeds and pericarps were made for the anti-trichomonal and cytotoxic activities determinations. The isolates were also detected by TLC in the methanolic extracts of the pericarp.

Anti-trichomonal Activity:

Trichomonas gallinae isolated from the pigeon was dropped into a test tube of normal saline. The solution was distributed into test tubes of Ringer's egg-serum culture for enteric protozoan and incubated at 37 °C for growth. Stock solutions of the isolates and Metronidazole (Flagyl, Aventis Pharma) in DMSO at the concentration of 20, 20 and 8 mg/ml, respectively, were made. Serial dilutions to 0.00, 1.953, 3.906, 7.8125, 15.625, 31.25, 62.5 and 125 mg/ml for the isolates and their derivatives, and 0.00, 0.1562, 0.3125, 0.625, 1.25, 2.5, 5.0, 10.0, 20.0 and 30.0 mg/ml for metronidazole with the fluid nutrient solution were used as the test agents. A 50 µL of each test agent and 150 µL of the nutrient solution were pipetted into the microwells and incubated in the steam incubatorat 37 °C for 24 and 48 h. The number of organisms per millilitre in each well for 0, 24 and 48 h were counted using the microscope. The experiments were done in triplicates (Narcisi and Secor, 1996, Adebajo *et al.*, 2004, 2006). The ~~E~~effects of the methanolic extracts of *M. koenigii* pericarp and seed as well as furocoumarins isolated from the seeds on this parasite were thereby evalauted.

Cytotoxicity:

The cytotoxicities of the methanolic extracts of the carbazole-producing leaves and stems and those of the seeds and pericarps of the furocoumarin-producing *M. koenigii* extracts were determined by haemagglutination activity using formaldehyde fixed bovine erythrocytes (Peumans, *et al.*, 1982; Sadiq *et al.*, 1989; Wang *et al.*, 1995). The isolates were not tested for cytotoxicity due to their low quantities.

3. Results

Anti-trichomonal Activity:

The anti-trichomonal activities of the extracts and isolates of the seeds and pericarps of this plant are shown in Table 1.

Cytotoxicitites of the Methanolic Extracts of the Leaf, Stem, Seeds and Pericarps:

The results for the methanolic extracts of the leaf and stem of the carbazolic-, seeds and pericarps of the furocoumarinic- *M. koenigii* are as given in Table 2.

4. Discussion

The present study reports the anti-trichomonal activities of the methanolic extracts of the pericarps and seeds of the furocoumarin-producing *M. koenigii* type and furocoumarins isolated from the seeds.

The methanolic extracts of the furocoumarin-producing *M. koenigii* seeds showed similarly high

Table 1: Anti-trichomonal Activities of Fruits Extracts and Isolates of the Furocoumarin-producing *M. koenigii*.

Extracts/Isolates	Inhibition of *T. gallinae* at 24 h		Inhibition of *T. gallinae* at 48 h	
	LC_{50} (µg/ml)	LC_{90} (µg/ml)	LC_{50} (µg/ml)	LC_{90} (µg/ml)
Seeds MeOH Extract	1.9	3.5	2.0	5.0
Pericarp MEOH Extract	2.0	3.5	2.1	3.6
Bergapten (C_{11}), ***1***	4.0	30.0	2.1	3.5
Imperatorin (C_{16}), ***2***	6.0	230.0	3.0	35.0
Isoimperatorin (C_{16}), ***3***	2.1	3.7	2.0	3.5
5-Methoxyimperatorin (C_{17}), ***4***	15.2	155.9	60.4	254.8
Heraclenin (C_{16}), ***5***	11.0	52.0	2.4	6.0
Byakangelicol (C_{16}), ***6***	22.0	61.0	2.1	3.6
Isogosferol (C_{16}), ***7***	2.0	5.2	2.0	3.5
8-geranyloxypsoralen (C_{21}), ***8***	22.0	125.0	2.7	42.0
Indicolatone (C_{21}), ***9***	2.1	3.8	4.3	7.4
β-sitosterol (C_{30}), ***10***	5.8	31.0	2.1	3.6
Metronidazole	1.9	3.5	2.0	5.0

LC_{50} and LC_{90}: Concentrations at which 50 and 90% parasites of *Trichomonas galliae* were killed; N = 3.

Table 2: Agglutination and Haemagglutination values of the methanol extracts of *Murraya koenigii*

Extracts	Concentrations (mg/mL) at which agglutination occurs	Haemagglutination Titre Value
Furocoumarin- producing type		
Seed	0.75 ± 0.03	0.34 ± 0.14
Pericarp	1.50 ± 0.00	0.67 ± 0.00
Carbazole- producing type		
Leaf	0.00 ± 0.00	0.00 ± 0.00
Stem	0.00 ± 0.00	0.00 ± 0.00

and comparable anti-trichomonal activities with those of the pericarp and Metronidazole, the standard anti-trichomonal agent used (Table 1). Similar high anti-trichomonal activities were obtained for the isolates isoimperatorin (***3***), isogosferol (***7***) and indicolatone (***9***) indicating that they were the main anti-trichomonal agents of the fruits. Generally, long exposure of the parasites to Metronidazole, the extracts and these isolates did not have any significant effect on their activities as shown by similar LD_{50} and LD_{90} values at 24 and 48 hours probably showing that they may be good substitutes for Metronidazole. Furthermore, long exposure of the parasites to the isolates of bergapten (***1***), imperatorin (***2***), heraclenin (***5***), byakangelicol (***6***), 8-geranyloxypsoralen (***8***) and β-sitosterol (***10***) showed lowered LD_{50} and LD_{90} values at 48 hours than the 24 hours showing that prolonged contact time of the compounds to the organisms was beneficial (Table 1) and clearly indicating that their activities were more likely to be cidal (total death) than static (Adebajo *et al.*, 2006).

On the other hand, 5-methoxyimperatorin (***4***) and ***9*** (a C_{10} furocoumarin with an 8-geranyloxy substituent bearing an extra lactone) have higher LD_{50} and LD_{90} at 48 hours than 24 hours. None of the furocoumarins isolated from the furocoumarin-producing *M. koenigii* gave a significantly higher activity than the MeOH extracts of the seeds or pericarps (Table 1) suggesting that these active compounds were probably working synergistically in the plant. Conversely, the carbazole alkaloids of the carbazole-producing plant with greater activities than the leaf and stem methanolic extracts were identified as the active compounds that were not working in synergism (Adebajo *et al.*, 2004, 2006).

Prenyl substitution at C-5 gave a better activity than at C-8 as shown by the higher activity of ***3*** over ***2*** respectively, indicating the probable importance of a free H-8 for activity. Elongation of ***2*** with another prenyl rest substituent only gave a better LD_{90} value for ***8*** (8-GOP) at 24 hours. However, the modification of the terminal prenyl rest in ***8*** with the introduction

of an oxygen atom and cylisation to form another lactone ring as in ***9*** greatly increased its activities above those of ***8*** at 24 and 48 hours. In fact, this modification in the structure of ***8*** brought the activity of ***9*** close to those of ***7***, the most active C_{16} furocoumarin with a C-8 oxygenation, the original seed MeOH extract and metronidazole. Hence, the presence of an additional α,β-unsaturated-γ-lactone in ***9*** (Adebajo *et al.*, 1997) that was absent in ***8*** may be responsible for the betterst activity of ***9*** over those of the other isolates. At 24 hrs, it gave same LD_{50} and LD_{90} values as Metronidazole. Generally, the presence of double bond(s) in the substituents of ***2*** and ***8*** gave poorer activities. Replacement of the double bond in the prenyl rest of ***2*** by an epoxy group in ***5*** gave better activities, especially at 48 hours. Although, ***7*** has a double bond similar to ***2***, the presence of a free alcoholic OH in its structure might have led to its better activities. Di-substitution of the psoralene nucleus as in byakangelicol (***6***) reduced the activites of the monosubstituted ***1*** and ***5***.

The results of the anti-trichomonal activities obtained in this present work confirmed the similarity between the carbazolic (Adebajo *et al.*, 2005, 2006) and furocoumarinic types of *M. koenigii*, and may therefore show that they are probably biological equivalents. This plant has already been established as a geographically race of the Curry plant, *M. koenigii* (Adebajo *et al.*, 1994 a, b; Adebajo 1997). Traditionally in Asia, only the leaf and fruits are eaten as spice and ethnomedicinaly as anti-dysenteric preparation. This present result may partly explain why the indigenes and other users did not differentiate these two races, as they would be more interested in the desired anti-dysenteric activity than in their chemical constituents. Metronidazole is the drug of choice for the treatment of amoebic dysentery. This present anti-trichomonal results for the fruits of *M. koenigii* coupled with its already reported activity against *E. histolytica* and anti-amoebic activities (Bhakuni *et al.*, 1969; Kapil, 1971; Kong *et al.*, 1986; Adebajo, 1997), should justifiesy the folkloric / ethnomedical use of the plant in the treatment of dysentery in Asia, especially that caused by *Entamoeba histolytica* and sensitive to Metronidazole. Furthermore, the demonstrated anti-trichomonal activities of the fruit show that the use of this plant as a spice would confer on the user (both humans and birds) additional protection against trichomonads or be useful in the management of trichomoniasis, especially by the low income earners found in the developing countries.

The low haemagglutination (HA) values ranging between 0.00 and 0.67 shown by all the extracts revealed their negligible cytotoxic effects (Table 2). However, the higher values (0.34-0.67) of the furocoumarin-producing plant indicates that it is relatively more toxic than the carbazole-producing one while the pericarp extract was also more toxic than the seed. The cytotoxicity of furocoumarins is already known (Murray *et al.*, 1982) and this may explain the relative toxicity of the extracts of the furocoumarin-producing plant. Although Nutan and co-workers (1988) have shown that the petroleum ether soluble fraction was the most cytotoxic, this relative non-toxicity of the carbazole-producing *M. koenigii* leaf (Table 2) confirms an earlier report of same (Adebajo *et al.*, 2006). Therefore, the use of the furocoumarin-producing plant as a substitute for *M. koenigii* in spicing foods would additionally give an anti-trichomonal activity similar to the authentic Curry Leaf.

Conclusion

The anti-trichomonal activites of the seed and pericarp methanolic extracts and their isolated furocoumarins of the furocoumarin- producing *M. koenigii* compares favourably with that of the standard drug Metronidazole. The active furocoumarins of the plant were working in synergism. This may therefore justify the folkloric use of this plant and its development as a potential chemotherapeutic agent.

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