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Research Article

MORINDA MORINDOIDES (BACKER) MILNE-REDH (RUBIACEAE): PHYTOCHEMISTRY, PHARMACOLOGICAL ACTIVITIES AND FUTURE DIRECTION: A MINI-REVIEW

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Abstract

The aim of this mini-literature review was to describe the traditional use, phytochemistry and biological properties of *M. morindoides*, a plant used as a conventional African medicine. In this investigation, the literature revealed that *M. morindoides* extracts were very efficient in the treatment of several diseases including malaria. According to our research, no studies have been conducted on the antisickling properties of *Morinda morindoides*. Further research is needed to assessment Antisickling activity of the different extracts of the parts of *Morinda morindoides*.

Keywords: Medicinal plant, *Morinda morindoides*, Traditional uses, Phytochemistry, Pharmacological activities.

INTRODUCTION

Nowadays, herbal medicine is an accepted and recognized form of medicine in the whole world (Mpiana *et al.,* 2020). The plant produces various secondary metabolites which are bio-synthetically derived from primary metabolites, and these compounds are the main source of herbal pharmaceutical products (Tshilanda *et al.,* 2019; Bongo *et al.,* 2019; Panzu *et al.,* 2020). The use of medicinal plants in therapy is a common practice in various parts of the world particularly in developing countries. According to the World Health Organization, a huge number of populations presently use phytomedicine for development of healthcare (Mohammed *et al.,* 2020).60% of the global population is using the traditional medicine system in order to overcome several health related issue (Mohammed *et al.,* 2020) and around 80% of African population use traditional medicine (Inkoto *et al.,* 2020a; Inkoto *et al.,* 2020b; Nkasa *et al.,* 2020). *Morinda morindoides* (Rubiaceae) has been greatly appreciated in recent times and researchers have found scientific support for its use in folk medicine. Traditionally, the parts of this plant species have various applications, ranging from treatment of malaria, diarrhea, amoebiasis, constipation, intestinal parasites, rheumatic pains and fungus (Cimanga *et al.,* 2006; Meite *et al.,* 2009; Zirihi *et al.,* 2010). Its parts of *M. morindoides* are reported to possess anti-inflammatory, cardiovascular, antimicrobial, antihypertensive, antihypoglycemic, anti-malaria, anti-spermatogenic, larvicidal, toxicological activities (Cimanga *et al.,* 2006; Adenubi *et al.,* 2010; Abdoulaye *et al.,* 2017).In this article, we present the data on *Morinda morindoides* and its major chemical compounds that could justify their use in the treatment of Sickle Cell Anemia in the Democratic Republic of Congo. In addition, the objective of the current study is to review the literature on phytochemistry and pharmacological activities of *Morinda morindoides*used in Congolese traditional medicine. This data would allow the use of this plant as a multifunctional and low toxicity drug candidate for the management of various diseases, including the Sickle Cell Anemia.

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METHODS

Search strategy

A non-exhaustive literature searches for relevant articles published in the last ten years was conducted in November 2020 on various electronic databases: Science Direct, Pubmed, Web of Science, Scopus, Google Scholar, POPLINE and System for Information on gray Litterature in Europe. As search strategy, the scientific name of this plant was used as a keyword, with the terms phytochemistry and Pharmacology. The chemical structures of *M. morindoides* naturally occurring compounds were drawn using ChemBioDraw Ultra 12.0 software package.

Eligibility criteria

In this literature mini-review, the selection of included studies was limited to studies with the inclusion criteria of:

(i) Phytochemistry data of *M. morindoides*,
(ii) Ethno pharmacological uses of this plant species in the past and clinical application,
(iii) Pharmacological properties of*M. morindoides* in human, *in vitro* assay, or *in vivo* model. In our research, the studies obtained were excluded based on several criteria such as unreliably extracted data, only-abstract available,
(iv) Overlapped data sets, reviews, thesis, editorials and book chapters.

RESULTS

Botanical description

Bagre et *al.*(2011) described *Morinda morindoides* (Fig.1) as a climbing liana, hairless with opposite leaves, elliptical oblong or elliptical obovate, wedge-shaped at the base. The leaves are 6-15 cm long and 3-8 cm wide. The leaf blade has about six pairs of lateral veins. The flowers, white in color, are grouped at the top, with the tube of the corolla short and robust. The fruits, bumpy, yellow when ripe, measure 4 cm in diameter.

Figure 1. Flowers and developing fruits of *M. morindoides*

Origin and geographic distribution

Morinda morindoides is distributed in a wide range of countries in West and Central Africa. It is native to Benin, Cabinda, Cameroon, Democratic Republic of Congo, Côte d'Ivoire, Nigeria, Liberia, etc. where it is called by several vernacular names such as Kongo bololo or Nkongabululu, Jologbo, ponju owiwi", zeleke, and brimstone (Akinloye *et al.,* 2015; Davis and Figueiredo, 2007).

Ethno-botanical uses

In southern African countries the parts of *Morinda morindoides*are used to treat many diseases. The decoction of its leaves is traditionally used to treat certain parasitic diseases such as diarrhoea, amoebiasis, constipation and malaria (Meite *et al.,* 2009; Zirihi *et al.,* 2010). In addition, several studies have reported therapeutic uses of this plant such as antiplasmodial, antispermatogenic, antifungal (Kabangu, 1990; Williamson 2001; Bagre *et al.,* 2006; Mbatchi *et al.,* 2006; Adenubi *et al.,* 2010; Koffi *et al.,* 2010).

Phytochemistry

Several compounds have been isolated and/or identified in this plant by several authors including sterols, triterpenoids, glycosides, flavonoids and iridoids(Fig.2). Cimanga et *al.*(1995 and 1999) isolated flavonoid aglycones and glycosides from ethyl acetate and n-butanol extracts from the leaves of *Morinda morindoides*. These include quercetin, quercetin-7, 4'-dimethyl ether, quercetin-3-rhamnoside, quercetin-3-rutinoside (4), kaempferol-3-rhamnoside, kaempferol-3-rutinoside, Kaempferol-7-rhamnosysophoroside, luteolin-7-glucoside, apigenin-7-glucoside and chrysoerol-7-neohesperidoside, kaempferol, apigenin, luteolin and chrysoerol. Eight iridoids were also isolated from ethyl acetate and n-butanol extracts from the leaves of this plant: gaiteroside, gaiteric acid, methoxygaiteroside, acetyl gaiteroside, epoxygaiteroside, epoxy methoxy gaiteroside, epoxy methoxy gaiteroside, dehydrogaiteroside, dehydromethoxygaiteroside (Cimanga *et al.,* 2003;2006). Cimnga et *al.* (2008) isolated two antraquinones, notably alizarin and chrysarin, from the chloroformic extract of the leaves of this plant. Leaves of *M. morondoides* extracted and isolated a ketosteroid from petroleum ether: [(22E)-2ß-hydroxy- 24- ethylcholesta- 4, 2,2- dien-3- one-1] (Harisolo *etal.* 2009). The work of Kouamé *et al.* (2010) has made it possible to highlight and identify, from the essential oils of this same plant species, fifty terpene compounds.

Biological activities

A. Antimalarial activity

Several antimalarial activities from *Morinda morindoides* were reported previously. Tona and Mesia (2001) evaluated *in vivo* antimalarial activity of ethanol, dichloromethane and lyophilized aqueous extracts of three plants, *Cassia occidentalis* (root bark), *Morinda morindoides* (leaves) and *Phyllanthus niruri* (whole plants) against *Plasmodium berghei* ANKA in mice. The result of this study indicated that dichloromethane extracts of this species have an antimalarial activity. Each lyophilized aqueous extract was less active than the corresponding ethanolic extract. Tona *et al.* (2004) reported *in vitro* antiplasmodial activity of seven ethanol extracts and twenty fractions of the partitioning of the initial ethanol extracts of seven African medicinal plants used in Democratic Republic of Congo (DRC) in treatment of malaria. The ethanol extracts from the leaves of *Morinda morindoides* ($50 < IC50 < 100$g/mL) were less active, but their petroleum ether fraction showed pronounced antiplasmodial activity ($IC_{50} < 3$g/mL). According to the authors, the observed antiplasmodial activity could be related to the presence of terpenes, steroids, coumarins, flavonoids, phenolic acids, lignans, xanthones and anthraquinones. Antidiarrheal activity. Meite *et al.* (2009) studied the effects of ethyl acetate extract of *Morinda morindoides* against castor oil-induced experimental diarrhea in albino Wistar rats. The results of this study indicated that at oral doses of 250, 500 and 1000 mg/kg body weight, the plant extract showed pronounced and dose-dependent antidiarrheal activity. The protective role of the extract at 1000 mg/kg was comparable to that of the reference drug, loperamide (5mg/kg). The extract (1000 mg/kg) produced a decrease in intestinal transit similar to that of atropine (5mg/kg), and significantly ($p<0.01$) inhibited castor oil-induced enteropathy.

B. Antiamoebic effect

Cimanga *et al.*(2006) evaluated the potential anti-amoebic activity and cytotoxic effect of aqueous decoction, 10 flavonoids and 4 iridoids isolated from 80% methanol extract of *M. moridoides* leaves against MT-4 cells. The results indicated that the aqueous decoction and the 80% Methanol extract showed interesting anti-amoebic activity with IC_{50} values of 3.1±1.7 and 1.7±0.6g/mL respectively. Apigenin-7-O-glucoside and luteolin-7-O-glucoside showed moderate anti-amoebic activity with IC_{50} values of 22.3±3.2 and 37.4±2.7g/mL, respectively. Kaempferol(IC_{50}=10.3±2.3g/mL), apigenin (IC_{50}=12.7±4.3g/mL) and luteolin (IC_{50} = 17.8±4.3g/mL) showed more pronounced activity than their corresponding glycosides. All iridoids tested showed very good activity with IC_{50} values below 10g/mL.

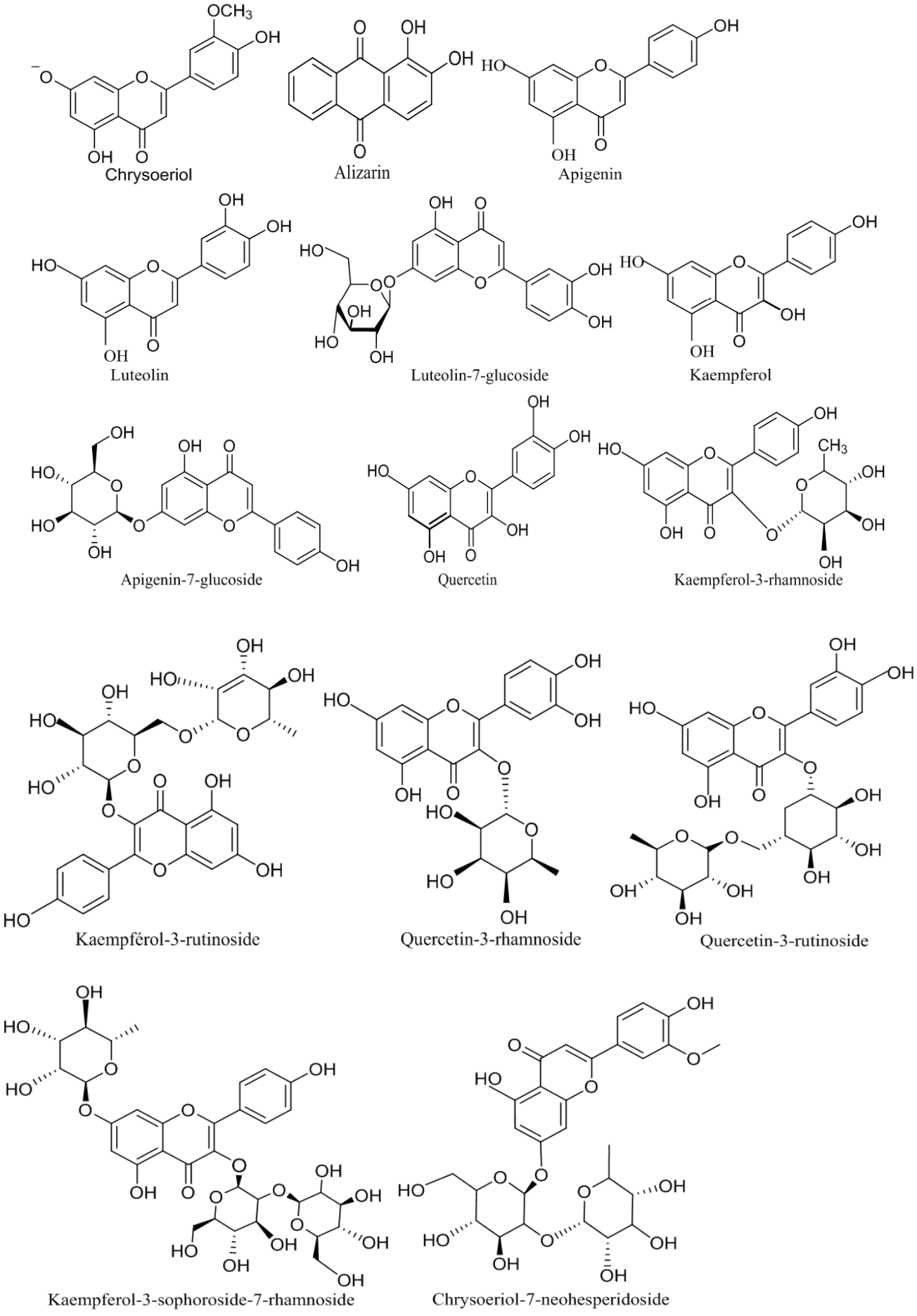

Figure 2. Cheminical structures of Morindamorindoides

The most active iridoids were epoxygaertneroside (IC_{50} = 1.3±0.4g/mL) and methoxygaertneroside (IC_{50} = 2.3±0.7), followed by gaertneroside and gaerneric acid with IC_{50} values of 4.3±1.8 and 7.1±1.4g/mL, respectively. Except for quercetin and 7,4-dimethyl quercetin ether which showed a cytotoxic effect with IC_{50} values ranging from 14 to 22 g/mL.In another study, Tona et *al.* [1998], in which several plants from the Democratic Republic of Congo were tested *in vitro* for their Antiamoebic activity, the aqueous extract from the leaves of *Morinda morindoides* showed a very high inhibitory activity (MIC=15.6 µg/mL).

C. Antibacterial activity

Antibacterial activity was evaluated used a soap containing hexane extract from *Morinda morindoides*leaves (Abdoulaye *et al.,* 2017). The results of this study showed that has the soap containing hexane extract of this plant have an antibacterial effect. The base soap had the lowest bactericidal effect with a MIC of 62.50 mg/mL for the two strains tested and MBC of 125.00 mg/mL and 62.50 mg/mL for *Staphylococcus aureus* and *Pseudomona aeruginosa* respectively. The results led to the identification of compounds all belonging to the anthraquinone family. The antibacterial activity of anthraquinone was tested against six strains of microorganisms using ofloxacin as standard (Moroh *et al.,* 2019). The minimum inhibitory concentrations+) recorded ranged from 8 to 128 µg/mL and *Staphylococcus aureus* was the most sensitive organism. Moroh *et al.* (2008) evaluated *in vitro* the antibacterial activity of the acetatic extract of fresh leaves of *M. morindoides* (Baker) Milne Redheat (Rubiaceae) on eight (8) strains of *Escherichia coli*, which are commonly found in diarrhea in children aged 0 to 5 years. Of these eight strains, three are reference strains namely *Escherichia coli* ATCC 25922, *Escherichia coli* ATCC 8739 and *Escherichia coli 2361*; three of known serotype (*Escherichia coli* O26H6, *Escherichia coli* O142 K86 and *Escherichia coli* O126 B16);isolated from well water and one of hospital origin. The extract was effective on all these strains. The Minimum Inhibitory Concentrations (MIC) recorded ranged from 3.75 to 15 mg/mL while the Minimum Bactericidal Concentrations (MBC) were found to be between 7.5 and 30 mg/mL. Considering this positive result, the authors recommend the use of *M. morindoides* leaves extract as a treatment for children's diarrhea.

D. Anti-spermatogenic activity

Adenubi et *al.* (2010) reported the antispermatogenic activity of aqueous extract of *Morinda morindoides* root bark on six male wistar rats. *M. morindoides* root bark extract caused a significant ($p<0.05$) reduction in sperm motility, a significant dose-dependent reduction in sperm count and a significant ($p<0.05$) dose-dependent increase in morphological abnormalities of sperm in treated rats. Thus, this study concludes that root bark extract of this plant has significant antispermatogenic effects on adult male Wistar rats, which may affect the reproduction of these male Wistar rats.

E. Cardiovascular activity

Gboko *et al.* (2012) investigated the properties of total protein extracts from the leaves of *Morinda morindoides* for rabbit blood pressure and mechanical activity of isolated rat hearts. The results showed that the total protein extract of *M. morindoides* has a blood pressure reducing effect (31.77 ± 2.72%) that would result from the combined actions of myocardial depression and muscarinic cholinergic receptor activation mediated by vascular smooth muscle relaxation.

F. Hypoglycaemic and hypolipidaemic activities

Olukunle et *al.*(2012) tested the hypoglycemic and hypolipidemic effects of *M. morindoides* root bark extracts and fractions. The aqueous and methanolic extracts were administered orally to 48 rats at a dose of 400 mg kg for 21 days. Fractions (hydromethanol, h hexane, chloroform and ethyl acetate) from bioactivity guided fractionation and A-F (CsF) subfractions of accelerated gradient chromatography were also evaluated in 45 rats for hypoglycemic activity at doses of 400 mg/kg, 200 mg/kg and 100 mg/kg respectively. Glibenclamide was used as a positive control. Polyoxyethylene sorbitan monooleate and distilled water administered to rats were used as negative controls. *Morinda morindoides* 400 mg/kg of aqueous and methanolic extracts and 100 mg/kg of chloroform CsF B caused (62.8%, 56% and 74%, respectively) reductions in blood glucose (BGL) levels. The aqueous extract caused a significant ($P < 0.05$) decrease in serum cholesterol values (133.48 ± 1.10) mg-dl ', low density lipoproteins (66.38 ± 2.50) mg/dL and a significant ($P < 0.05$) increase in high density lipoproteins (51.0 ± 3.0) mg/dL compared to control.

G. Antifungal activity

Bagre *et al.* (2006, 2011) reported that ethyl acetate extract of *M. morindoides* leaves possess antifungal effects against *Cryptococcus neofoman* with IC_{50} of 1.35 mg/mL. Touré et *al.*(2010) developed a soap formulation based on hexane extract from the leaves of *Morinda morindoides* in order to evaluate its antifungal activity against human-derived fungalisolates. The result showed that *M. morindoides* extract soap inhibited the growth of all fungal strains at a MIC of 31.25 mg/mL. In addition, the base soap (control) also *Candida albicans* at a MIC of 125 mg/mL and at a MIC of 62.50 mg/mL for the other 3 strains tested.Touré et *al.* (2011) compared the antifungal activity of various extracts (aqueous, ethanol, ethyl acetate and hexane) of *M. morindoides* and performed phytochemical screening. The results showed a higher antifungal activity of the hexane extract against *C. albicans* with a MIC of 31.25 mg/mL and IC_{50} of 6.17±1.04 mg/mL compared to the other extracts (aqueous, ethanolic and acetate). The same extract showed the highest activity against *T. rubrum* with a MIC of 15.62 mg/mL and an IC_{50} of 2.68±1.19 mg/mL.

H. Cytotoxicity

Regarding cytotoxicity effect, Marie-Genevieve et *al.* (2010) claimed that toluene extract of *M. morindoides* leaves dispayed a potent effect on P388 and L1210 cells with IC_{50}=6.0 and 6.5 µg/mL, respectively, while K562 cells were slightly less sensitive to the exposure of toluene extract 12.2 µg/mL. Nevertheless, extraction with methyl tert-butyl ether (MtBE) was less efficient than toluene extract in all tested cell lines. The effects of toluene and MtBE extracts in K562 human erythroleukemia cells may be due to apoptotic induction. On MT4 cells, Cimanga *et al.* (2006) reported that quercetin and quarcetin-7, 4'-dimethylether produced cytotoxic effect with CC_{50} ranging from 14 to 22µg/mL. Interestingly, *M. morindoides* appeared not to damage normal cells. At high

concentration of 150 µM, some phenylpropanoid conjugated iridoids caused 13.4% cytotoxic in maximum (Zirihi *et al.,* 2005). Boga *et al.* (2105) indicated that, dichloromethane-ethanol extract of this plant, showed relativy low toxicity in normal rats with LC_{50} within 200-5000 mg/kg. Moreover, with doses ranging 50-100 mg/kg, this extract exerted no significant effect on body weight, biochemical parameters and blood parameters. Unfortunately, these studies used different extracts from *M. morindoides*, in which constituents were not specified so that we could not conclude whether *M. morindoides* only caused toxicity on abnormal cell lines.

Conclusion

In the current mini-review the aim was to review the literature on the traditional use, phytochemistry and biological properties of this valuable plant species. The results of this bibliographic investigation revealed that *M. morindoides* contains pharmacologically active substances as sterols, triterpenoids, glycosides, flavonoids and iridoidspharmacologically active substances with antidiarrheal, antimalarial, Antispermatogenic, antiamoebic properties. According to our research, no studies have been conducted on the antisickling properties of *Morinda morindoides*. Further research is needed to assessment Antisickling activity of the different extracts of the parts of *Morinda morindoides*.

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