Biomedicine & Pharmacotherapy 108 (2018) 457–466

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Moringa oleifera and their phytonanoparticles: Potential antiproliferative agents against cancer

Charlette Tiloke[a,b], Krishnan Anand[a], Robert M. Gengan[b], Anil A. Chuturgoon[a,*]

[a] Discipline of Medical Biochemistry and Chemical Pathology, School of Laboratory Medicine and Medical Sciences, College of Health Sciences, University of KwaZulu-Natal, Private Bag 7, Congella, Durban, 4013, South Africa

[b] Department of Chemistry, Faculty of Applied Sciences, Durban University of Technology, Durban, 4001, South Africa

ARTICLE INFO

Keywords:
Moringa oleifera
Gold phytonanoparticles
Cancer
Antiproliferative
Apoptosis

ABSTRACT

Cancer is classified as one of the leading causes of global mortality. It has affected millions of people, often with poor prognosis. Having severe side-effects with conventional chemotherapy, alternate drugs and therapies are actively being investigated. There is a need for innovative drug discovery and design as existing cancer therapies are costly and not readily available. Ayurveda and traditional medicine have utilised natural resources such as plants and trees as part of their regime to treat various illness and diseases with positive outcomes. One such tree is *Moringa oleifera* (MO). Almost all parts have shown to be effective against several ailments including cancer which was attributed to the bioactive constituents. Targeted therapies had led to the development of nanoparticles which are extremely effective in various biomedical applications due to their small size. Green synthesis of gold nanoparticles have great potential as naturally occurring plants and trees such as MO can be used in the synthesis process. The resultant gold phytonanoparticles are useful in cancer therapies with improved survival rates and quality of life. The review highlights the importance of MO in natural medicine, synthesis of phytonanoparticles and the fundamental role as a potential antiproliferative agent against cancer.

1. Introduction

Natural traditional medicine, still actively practiced worldwide, has been part of many lives through several generations [1]. Although Western medicine has revolutionised health-care, many pharmaceutically active drugs are being developed based on natural resources (e.g., plants) as they provide many bioactive components [1]. As conventional therapies are relatively expensive and accessibility is a major concern especially in third world countries consisting of huge rural populations, natural plants and trees have provided the necessary resource to supply their demand as either food or medicinal use for treatment of various diseases including cancer [1].

Natural medicinal plants are found throughout the world [2]; natural medicinal products are readily available, easily ingested, relatively non-toxic and cost-effective [2]. Approximately 70% of available and approved drugs have been developed from these natural resources [2]. The use of medicinal plants for formulation is beneficial as their bioactive constituents have an impact on multiple biological signalling pathways [2]. They can act in synergism to produce a desired therapeutic outcome [2]. This can be seen to be effective in comparison to a single dose of a compound [2]. However, investigations into the quality, safety and efficacy of these natural medicines are imperative in the development as alternate therapeutic agents [2].

Novel cancer agents are imperative to combat the existing problem of drug-resistance, side-effects and costs. Natural products have inspired the development of anticancer agents [1]. These include terpene paclitaxel from *Taxus baccata* and Vinca alkaloids from *Catharanthus roseus* [1]. There are many plants that are yet to be explored for their

Abbreviations: ARE, antioxidant response element; CPT1, carnitine palmitoyltransferase I; CPTII, carnitine palmitoyltransferase II; associated 9 (Cas9), clustered regulatory interspaced short palindromic repeat (CRISPR); DEN, diethyl nitrosamine; DMBA, 7, 12 dimethylbenz (a) anthracene; GMG-ITC, glucomoringin derived-isothiocyanates; GST, glutathione *S*-transferase; AuNPs, gold nanoparticles; gRNA, guide RNA; HO1, heme oxygenase 1; hnRNPs, heterogeneous nuclear ribonucleoproteins; HDR, homology-directed DNA repair; IAPs, inhibitors of apoptosis proteins; MO, *Moringa oleifera*; NFκB, nuclear factor kappa B; Nrf2, nuclear factor (erythroid-derived 2)-like 2; NQO1, NAD(P)H:quinone oxidoreductase 1; NHEJ, non-homologous end-joining; PAM, Protospacer Adjacent Motif; ROS, reactive oxygen species; Smac/DIABLO, second mitochondria-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low PI; SA, South Africa; AgNPs, silver nanoparticles; SR, Ser/Arg rich; TEM, Transmission Electron Microscopy

* Corresponding author.

E-mail addresses: TilokeC@ukzn.ac.za (C. Tiloke), KrishnanA@ukzn.ac.za (K. Anand), genganrm@dut.ac.za (R.M. Gengan), chutur@ukzn.ac.za (A.A. Chuturgoon).

https://doi.org/10.1016/j.biopha.2018.09.060
Received 25 April 2018; Received in revised form 10 September 2018; Accepted 11 September 2018

biological activities. *Moringa oleifera* (MO) is a traditional medicinal tree which has shown great potential in complementary and alternate medicine [3]. MO has been used traditionally for the treatment of hyperglycaemia, inflammation, bacterial/viral infections and cancer [4]. MO has a high content of antioxidants and bioactive compounds that play an important role in their efficacy [4].

Nanotechnology has revolutionised modern medicine; it has several characteristics which impact on their mode of action [5]. Nanoparticles are relative small with a large surface area [5]. Green synthesis of nanoparticles utilises plant extracts as reducing agents [5]. The plant used during the synthesis process plays an important role as it contributes/influences the resultant nanoparticle characteristic [5]. The plant extracts, in general, are rich in polyphenols and bioactive compounds which aid in the reduction process [5]. MO is abundantly rich in polyphenols which can be used in the synthesis of phytonanoparticles [5]. This review aims to outline the importance of natural medicines and phytonanoparticles from MO as potential antiproliferative agents against cancer.

2. *Moringa oleifera* – nature's gift

Moringa oleifera (MO), originally found in India [2], is now located across the world including SA [6]. It belongs to the family Moringaceae [6]. It is unique with great potential highlighted by the National Institute of Health [2]. The plant is highly valued as almost all parts are used as a food source, as well as in the traditional treatment of various ailments and to promote good health [2]. These parts include but not limited to the leaves, flowers, seedpods, seeds, roots, bark and gum [2]. It is used traditionally to treat bronchitis, infections and fever amongst several other illnesses [2]. It also displays antioxidant, antibacterial, antifungal, antidiabetic, neuroprotective, cardioprotective and anti-inflammatory properties [2]. MO is known to modulate the immune system [2]. It has also shown to have diuretic and cholesterol lowering activity [7]. In addition, MO is hepatoprotective, increases the rate of wound healing and are antihypertensive [7]. MO improves function of the liver and kidneys and regulates the thyroid hormone [6].

MO belongs to the family *Moringaceae* and is commonly referred to as the Drumstick tree, Miracle tree or Horseradish [7]. There are 13 species however MO is the most cultivated with height ranging between 5–10 m (Fig. 1) [6]. The tree grows rapidly and has drought resistance properties therefore can be grown in tropical, subtropical and arid regions of the world [7].

The safety and efficacy of natural medicinal plants such as MO is imperative for continued traditional and conventional use. The aqueous leaf extract were assessed for safety in rats [9]. Various doses were assessed acutely and chronically. It was determined that intake of MO leaves up to 2000 mg/kg is relatively safe. Asiedu-Gyekye et al., 2014 also assessed acute (5000 mg/kg) and sub-acute (40–1000 mg/kg) toxicity in rats [10]. No adverse effects was seen however there was an elevation in liver enzymes. It was concluded that the leaf extract is safe and consumption should not exceed 70 g/day.

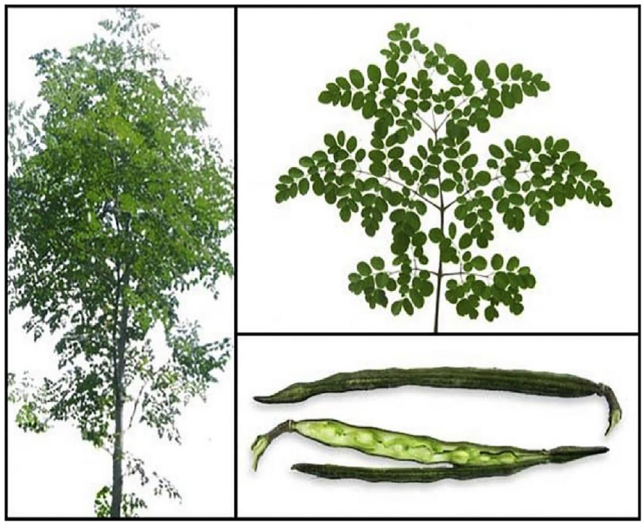

Fig. 1. *Moringa oleifera* tree, leaves, seedpod and seeds [8].

Table 1
Comparison of the nutritional content in MO leaves [2].

Nutritional Content	Nutritional value	Comparison
Vitamin A	4x	Carrots
Vitamin C	7x	Oranges
Potassium	2x	Bananas
Iron	>	Spinach
Protein	>	Egg
Calcium	>	Milk

3. Nutraceutical properties of *Moringa oleifera* – potential use in cancer cachexia

The tree is grown as a food and medicinal source [7]. Due to its nutritional properties, the leaves are used in the herbal formulation of tea [2]. The leaves can also be used raw, cooked, or powdered and still retain its nutritional content. In addition, the leaves are preferred due to the following nutritional properties (Table 1):

The nutritional property of MO varies due to the environment, cultivation methods and genetic background which influences their content [7]. It is a rich source of phosphorous, folic acid, β-carotene and glutamic acid. The leaves contain high levels of nutrients which are required for growth and development which can be beneficial in developing countries where malnutrition is prevalent [6,11]. MO has grown well in both rural and urban settings therefore a vital sustainable source for malnutrition. MO has a good source of phytosterols such as sitosterol, kampesterol and stigmasterol [11] which enhances estrogen production.

High levels of vitamin A, C, and E is present in MO leaves [6]. Vitamin A plays a key role in vision, immunity, cell growth and differentiation and reproduction. Vitamin C and Vitamin E assist in protection against free radicals therefore serve as good source of antioxidants. In addition, MO has a high content of terpenoids, anthraquinones and glycosides [11]. The seedpod is fibrous and therefore aid in digestion. The seedpod, leaves and flowers have 30%, 44% and 31% amino acid content respectively. Oleic, linoleic and linolenic acid are present at 76% in MO seed oils comparable to olive oil.

MO contains a natural source of important bioactive compounds which act synergistically in its therapeutic effect. An inflammatory response in various diseases is a result of an increase expression of nuclear factor kappa B (NFκB), cytokines (pro-inflammatory IL-1β, IL-6 and TNF-α) and nitric oxides [12]. It is also a host defence mechanism. In addition, nuclear factor (erythroid-derived 2)-like 2 (Nrf2) also plays a vital role by upregulating antioxidant and chemopreventive genes. Nrf2 inhibits the inflammatory response. Nrf2 mode of action is a result of exposure to an environmental/chemical stress and increase in reactive oxygen species (ROS) which causes Nrf2 to translocate to the nucleus [12]. It binds to the antioxidant response element (ARE) where it cause the transcription of important genes such as glutathione S-transferase (GST), NAD(P)H:quinone oxidoreductase 1 (NQO1) and heme oxygenase 1 (HO1). Anti-inflammatory drugs have several health risks therefore alternate drugs are investigated. MO seeds have shown to have antioxidant and anti-inflammatory activity due to the nitriles, glycosidic glucosinolates, isothiocyanates, carbamates and thiocarbamates. 4-[(α-L-rhamnosyloxy)-benzyl] glucosinolate (glucomoringin) is found in the seed extract and is converted by myrosinase to form its corresponding 4-[(α-L-rhamnosyloxy)-benzyl] isothiocyanate. Their