



Unearthing the Medicinal Properties of *Tillandsia recurvata* (Ball Moss): A Mini Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors HICL and JB designed the study and wrote the protocols. Authors NJT and CTW carried out experiments. Author SB wrote the first and final drafts of the manuscript. All authors read and approved the final manuscript.

Mini-review Article

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ABSTRACT

Background: More than half of traditional medicines are of natural origin and research has shown that these are associated with fewer side effects than the synthetic ones, since less than 10% of the 350,000 identified plant species have been exposed to some amount of bioactive screens, it is now the aim of researchers to screen more plants and also identify the active ingredients responsible for detected bioactivities. These we believe may provide the foundation for identifying new drug leads that may prove useful against chronic lifestyle diseases. This review takes a look at the work that has currently been conducted on *Tillandsia recurvata* commonly known as ball moss which is believed to assist with future research.

Results: The chloroform, methanol and water extracts of ball moss have shown cytotoxicity against several human cancer cell lines and the methanol extract induces apoptosis in some. Further the chloroform extract was shown to reduce angiogenesis and the methanol extract inhibited particular kinases (CSNK2A2, MEK5, GAK, FLT and DRAK1) of which MEK5 and GAK have been implicated in prostate cancer. The same

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extract was further shown to display promising anti-diabetic properties via a reduction in fasting blood glucose ($P < 0.05$), fructosamine levels ($P < 0.05$), serum CRP and insulin levels when compared to the control mice. Phytochemical screens identified a novel glycoside and several cycloartanes and dicinnamates; 1,3-di-O-Cinnamoyl-glycerol and (E)-3-(cinnamoyloxy)-2-hydroxypropyl 3-(3,4-dimethoxyphenyl)acrylate. Further bioactive screens on these isolates showed that cycloartane-3,24,25-triol reduced the viability of prostate PC-3 and DU145 cell lines. This isolate was further shown to inhibit MRCK α kinase implicated in the initiation and progression of prostate cancer.

Conclusions: This review confirms the promising efficacy of the *T. recurvata* plant and so its worth for further research which may prove useful in the pharmaceutical and nutraceutical industries. Such benefits have already begun with the introduction of the alpha prostate formula, now on the market for improved prostate health.

Keywords: *Ball moss; Tillandsia recurvata; anti-cancer; diabetes; kinase inhibition; cytotoxic.*

1. INTRODUCTION

Even though recent developments have been made over the last decade in the advancement of new drugs vis-a-vis genetics, biotechnology and genomics, still, natural products remain vital to the New Era. There has been a recent and renewed interest in the advantageous properties of natural products for the treatment and prevention of chronic diseases. An approximated 80% of the world's population depend primarily on natural plant products which are either sold as herbs, food supplements or drugs [1]. Of the top 50 drugs sold in European pharmacies, statistics show that roughly 50% of these are based on or are derivatives of natural products [1].

It is then not surprising when the statement is made that much of the wealth of a country resides in its plant inheritance, whether the plants are endemic, naturalized or recent introductions [2]. And even with that knowledge only about 10% of the existing 350,000 plant species known worldwide have been screened for biological activity [3]. Of these, Jamaica accumulates roughly 2888 with approximately 30% endemism [4]. Jamaica is known for its profound reliance on the usage of herbal plants to treat illnesses as evidenced in a report by the Tropical Metabolism Research Unit (TMRU) of the UWI, Jamaica, where 71% of patients reported using herbal remedies before seeing the doctor [5]. This is however becoming an increased concern as more and more information is revealed about drug interactions. It would be nonetheless a safe assumption to make that if adverse events and interactions amongst herbs, drugs or both are of concern, then it would be blatantly visible given the copious usage of these products. On the other hand, pharmacokinetic and pharmacodynamics data is lacking for many botanical and nutritional supplements. The adverse event reporting systems that are presently in place for drugs are inadequate for monitoring dietary supplement products given the vast number of complex and unique formulations [6]. As a result acquiring a better understanding of traditional medicine, evaluating its phytochemical constituents, its impact on drug metabolising enzymes and ultimately its incorporation in modern medical practise has been the preferred and safer route to ensuring the health and well-being of all individuals [2,7-9]

This review explores the bioactivity of the ball moss plant, a plant that is currently being researched by our laboratory. Since the introduction of *in vitro* high-throughput screening protocols, laboratories are now able to carry out a wide array of bioactive screens even though it isn't always feasible to define and choose the appropriate target for any given

disease [3]. Because of this, our laboratory has conducted varying bioactive screens and published several manuscripts, nonetheless, it helps to have access to as much of the bioactivity data in one paper as it can provide insight into the direction to be taken to expedite the production of new drug leads.

Tillandsia recurvata L. a flowering plant of the pineapple family Bromeliaceae, commonly called the Jamaican Ball Moss (Fig. 1), the Old Man's beard or Scorn of the Earth is one of the several important medicinal plants found in Jamaica. The plant is an angiosperm (not a moss) and is widely distributed throughout North America, South America and the Caribbean [10]. Ball Moss is an epiphyte that grows mainly on Mango trees, Oak trees and on telephone and electrical lines. Because of the nature of the growth of epiphytes, Benzing [11,12] characterized these plants into two functional groups based on their access to water; continuously supplied and pulse supplied epiphytes. The former comprises of tank bromeliads and taxa of which ball moss belongs, these have access to a constant supply of moisture while the latter group known as the bark epiphytes succumb to water stress if they don't have rain for a couple of hours at a time [11].



Fig. 1. The epiphyte, ball moss growing on a tree

Since they have no access to the soil, epiphytes lack direct contact to the most important nutrient source that ground rooted plants have access to, notwithstanding, epiphytic plants obtain their nutrients from the plants upon which they grow, the rain, dust and intercepted mist [13]. Research has placed emphasis on the rain water as a supply of nutrients since it acts as a vehicle for inorganic salts and organic molecules including nitrogenous compounds [14, 15]. Further, Benzing showed that small organic nitrogen molecules could be absorbed through the trichomes [16]. Evidence of nitrogen fixation in the *Tillandsia* species confirms the presence of nitrogen-fixing micro flora and this process can contribute greatly to the nitrogen nutrition of the plants [15,17,18]. Ball moss and other epiphytes obtain their nutrients from unusual morphological features such as; phytotelmata, litter-trapping leaf arrangement, bromeliad trichomes and orchid velamen radicum [13,19]. The plant does not harm the tree on which it grows due to the symbiotic relationship of both angiosperms unless it grows profusely to shade the tree from sunlight.

The plant is characterized by the presence of a rudimentary root system and shoots having 5-8 linear leaves forming a rosette, covered with peltate, absorptive trichomes [11]. It forms a tangled mass of leaves and aerial roots, which are dry and grey colored and turns green when exposed to moisture. Older plants develop multiple ramets which form a spherical tussock ranging in size from a golf ball up to the size of a basketball, hence the common name "ball moss" [11,12]. Due to its abundance and wide distribution through the island, our scientists decided to investigate the bioactive worth of the ball moss plant.

2. DISCUSSION

2.1 Use in Ethnomedicine

Even though there is no official report that the Jamaican Ball Moss is used in Jamaican ethnomedicine, several countries have reports of its use in their ethnomedicinal practices (Table 1). The major reported use is in Brazil where the plant is used against rheumatism, ulcers and hemorrhoids [20-22].

Table 1. Ethnomedicinal uses of *Tillandsia recurvata*

Country	Uses	Part used	Reference
Bolivia	Kidney inflammation	Leaf	[23]
Brazil	Against rheumatism, ulcers and haemorrhoids	Entire plant	[20-22]
	Bloodshed (stop bleeding)	Entire plant	[24]
Mexico	Menstrual regulation	N/I	[25]
	Animal fodder	N/I	[26]
Uruguay	Antispasmodic, eye infection	Aerial part	[27]
USA	Leucorrhoea	Entire plant	[28]

2.2 Pharmacological Effects of Ball Moss

Ball moss has shown interesting anticancer, antimicrobial and anti-diabetic assays. These activities are enumerated below and in (Table 2).

Table 2. A summary of the pharmacological activity of *T. recurvata* and its isolates

Extract/compound	Study	Activity	Reference
Methanol extract	Kinase inhibition	Kd ₅₀ CSNK2A2=14µg/ml DRAK1 =12µg/ml FLT3 =12µg/ml GAK=8µg/ml MEK5 =12µg/ml	[29]
Chloroform extract	Antiangiogenesis (Ex –vivo rat ring aorta)	30 µg/ml	[30]
Compound 1 (Fig. 2)	Antiangiogenesis (Ex –vivo rat ring aorta)	10 µg/ml	[30]
Compound 2 (Fig. 2)	Antiangiogenesis (Ex –vivo rat ring aorta)	>30 µg/ml	[30]
Compound 8(Fig. 2)	Kinase inhibition and anti-cancer	Kd ₅₀ for MRCK =0.26 µMα	[31]
Chloroform extract	Cytotoxic to A375(Human melanoma) MCF-7 (Human breast)	IC ₅₀ =0.9 ± 0.40µg/ml IC ₅₀ =40.51±10.66 µg/ml	[31, 32]
Methanol extract	PC-3 (Human prostate) Cytotoxic against PC-3, breast cancer Kaposi sarcoma, B-16 melanoma and a B-cell lymphoma	IC ₅₀ =5.97 ± 4.99µg/ml IC ₅₀ s>2.5 ± 4.99µg/ml	[33]
Water extract	Antimicrobial towards <i>E. coli</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>B. subtilis</i>	Active at 10mg/ml	[27]
Organic solvent extracts	Antimicrobial towards <i>S. aureus</i> , <i>S. typhi</i> , <i>P. mirabilis</i> , <i>S. flexneri</i> , <i>E. coli</i>	Active at 100µg/ml	[27]

2.2.1 Anti-cancer potential of ball moss extract

Being the third leading cause of death worldwide, cancer [34-36] is a broad group of diseases all involving de-regulated cell proliferation and is projected to claim the lives of 26 million persons by 2030, of which 17 million will die per annum [37]. Most recent statistics from the Jamaica Cancer Society Registry (covering the period 1993-1997) state that roughly 43.2 per hundred thousand of the female population were diagnosed with breast cancer. Additionally, Jamaican men have arguably the highest reported cases of prostate cancer in the world [38]. With alarming statistics like these it is understood why so many research groups have made resolute most if not all of their resources, into investigating cancer, in hopes of finding the ideal drugs that will attract as little side effects as possible. *In vitro* research conducted in our lab showed that a crude chloroform extract of the Jamaican ball moss was cytotoxic against five human cancer cell lines; A375 (melanoma), BC (breast), DU-124 (prostate), MCF-7 (breast) and PC-3 (prostate cancer), [32]. Additionally, more recent studies have showed that the methanol extracts were cytotoxic against five histogenic

cancer cell lines; PC-3 (prostate), MCF-7 (breast), Kaposi sarcoma, B-16 melanoma and a B-cell lymphoma from a transgenic mouse strain with IC₅₀s > µg/ml with apoptotic mechanistic cell viability reduction [33].

In searching for natural lead molecules that possess effectiveness against selected cancers, it is important that one has a fair idea of the processes involved in tumour growth as this will guide researchers into the appropriate bioactive screens to execute which will offer insight into the effectiveness of the tested entity. It is then understood that whilst finding molecular entities that are cytotoxic towards cancer cells is favourable, it cannot be enough. Benign tumours are those that are confined to one area and as such are not considered cancerous as they do not pose a threat to the individual. However, when the tumour begins to metastasize, that is, it begins spread and invades neighbouring tissues; it is considered cancerous as its threat to the individual is exponentially augmented with every incremental increase. One contributing factor towards the increase in tumour growth is the process of angiogenesis, which is the physiological growth of new blood vessels from pre-existing ones. This provides an ideal environment for the tumour as it is fed with the appropriate nutrients so facilitating its growth. Tumours starved of angiogenesis will remain benign for an indefinite period while those exposed experience a rapid exponential growth [39,40]. It is therefore prudent to investigate molecular entities that are not just able to reduce cancer cell viability but also angiogenesis as well. Results from our lab showed that the crude chloroform ball moss extract was not just cytotoxic against human cancer cell lines but it also reduced angiogenesis as well [30] which means that it tackles the phenomenon of cancer from not just one but two angles so making this plant an even more promising screening agent against cancer.

Normal cellular growth is tightly regulated and various checkpoint systems are in place to ensure the transition of healthy cells from one point in the cell cycle to the next. These checkpoint systems such as cyclin dependent kinases are equipped to identify genomic alterations within the cell and initiate fixing this before the cell is allowed to multiply [41,42]. In the event the identified problem cannot be fixed, the cell can induce its own death also known as apoptosis. Cancer initiation can be caused when the checkpoint systems themselves are not functioning as they should, be it via the process of carcinogenesis or hereditary. When this occurs, there is no mechanism in place to initiate problem solving or apoptosis. It has therefore become a recent and therapeutically relevant direction to identify molecular entities, be them inducers or inhibitors that can regulate particular kinases in hopes of restoring the normal balance to cell proliferation [43]. This is believed to provide a solution to cell uncontrollable growth evidenced in malignant tumours. Of the four hundred and fifty one kinases investigated in our lab, the ball moss selectively inhibited 5 (CSNK2A2, MEK5, GAK, FLT and DRAK1) and obtained Kd₅₀s were below 20 µg/ml [29]. Since MEK5 and GAK kinases have been associated with aggressive prostate cancer, the inhibitory properties of the ball moss against them coupled with its previously found bioactivity towards PC-3 cell line and its ability to reduce angiogenesis makes it even more promising in the arena of drug discover towards prostate cancer among others. Due to these promising data, a nutraceutical was developed by our lab known as the Alpha Prostate Formula 1. This product we believe will promote the health of men's prostate in addition to providing protection against prostate cancer.

2.2.2 Anti-diabetic potential

Type II diabetes accounts for roughly 90% to 95% of all diagnosed cases of diabetes [44] and in general, diabetes affects 6 to 20% of the population in the Western industrialized

societies and was estimated to have claimed 150 million people in 2000 with an increase to 220 million in 2010 [45,46]. Due to the chronic hyperglycaemia experienced by this disorder, persons with the disease are prone to developing conditions such as; retinopathy, neuropathy, vascular diseases and these are mainly responsible for morbidity and mortality observed in diabetic patients [44,47]. Further, Type II diabetes is concomitant with prolonged inflammation, and it is hypothesized that this could be enabled by a pathway that involves a cytokine-mediated acute-phase response inflammatory process [48,49]. C-reactive protein (CRP) is an acute-phase reactant produced under the stimulation of adipocyte-derived pro-inflammatory cytokines, such as IL-6 and TNF- α making it an ideal marker for the subclinical inflammation [50]. Results from our lab indicated that experimental rat models fed with diets containing ball moss extracts showed a significant reduction in fasting blood glucose ($P < 0.05$), fructosamine levels ($P < 0.05$), serum CRP and insulin levels as compared to the control mice. These preliminary findings imply that *Tillandsia recurvata* may prove effective in improving diabetic indices and could pave the way for novel therapeutic and pharmaceutical interventions for treatment and management of type II diabetes.

2.3 Phytochemistry

A number of phytochemicals present in the ball moss plant have already been identified and characterized (Fig. 2). A few of these have been linked to some of the observed bioactivity of the plant (Table 2). While our research group isolated compound 5 (cycloartane diol), previously isolated compound 8 (cycloartane triol) was also investigated by our group and was shown to be bioactive against our screens as seen in Table 2. Due to the increased understanding of adverse drug interactions, modern medicine is inclined to identifying key phytochemicals that are effective in treating chronic ailments as opposed to plant extracts. As previously mentioned, monitoring drug interactions is more feasible when a key constituent is administered rather than many. Even though there is the theory that plant extracts could be more effective biologically due to the synergistic effect amongst their phytochemicals, one begs to argue whether the benefit outweighs the possible risks if any. Given that it is an expensive and time consuming exercise to identify all bioactive metabolites in a plant, scientists have resorted to screening plants with potential medicinal application for safety as well as standardizing crude extracts on the basis of identified chemical markers. (Fig. 2) also represents other compounds (Compounds 4,6-7) that have been identified from the ball moss plant whose bioactivities are yet to be identified but could serve as chemical markers or metabolomics fingerprints of the plant [51,52].

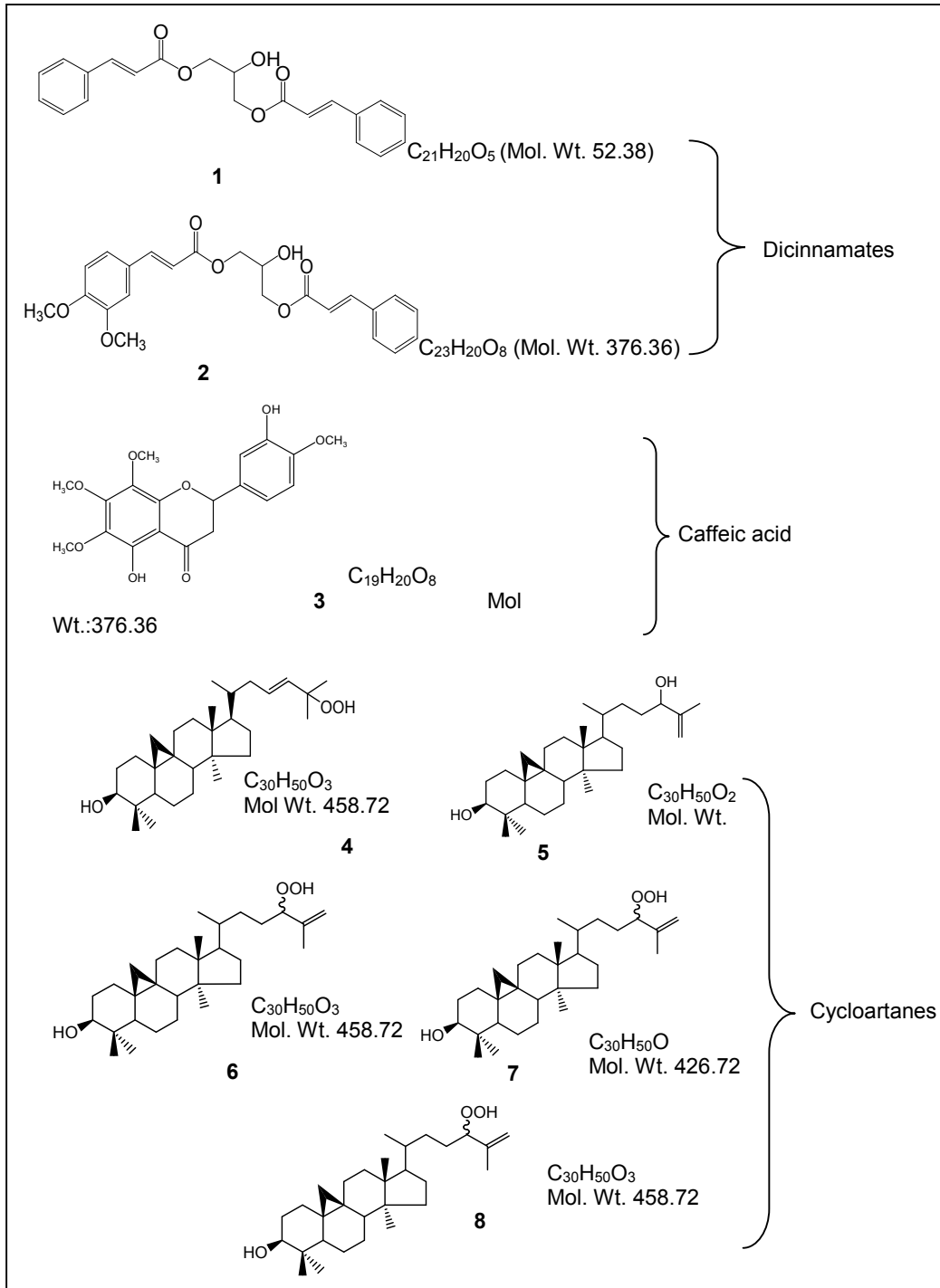


Fig. 2. Major compounds isolated from ball moss

3. CONCLUSION

This paper has summarized available information on the ethnomedicine, pharmacology and phytochemistry properties of Ball Moss, some of which have led to the alpha prostate formula which is now used to enhance prostate health. Given the identified folklore usage and promising pharmacological and phytochemistry potential of this plant, there remains much work to be done. Future research is thus recommended in the following areas: ethnomedical surveys to document hitherto unrecorded folk uses, screening other *in vitro* and *in vivo* assays for efficacy and safety as well as phytochemical analysis to isolate bioactive or marker compounds. A combination of chromatographic techniques as well as metabolomics analysis will be useful in future phytochemical analysis.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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