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Bioactivity of Mesona palustris (Black Cincau) as a Nutraceutical Agent

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Abstract: Mesona palustris, colloquially known as 'Black Cincau', can commonly be found in East and South East Asian regions. Traditionally, M. palustris extracts have been used as herbal drinks to promote vitality and health. With advancements in technology, M. palustris may now be processed into more nutraceutical options, including edible jellies. Studies have also come up with efficient extraction processes to better characterize its chemical constituents. Containing phenolic compounds like flavonoid and tannins, M. palustris has recently been reported to yield many exciting pre-clinical observations that are comparable to bioactive metabolites found in plants from the same genus, including Mesona procumbens and Mesona chinensis, alongside unrelated herbaceous plant species which have been utilized as natural remedy options. Thus, this review discusses the recently observed pre-clinical applications of M. palustris by highlighting its ability in promoting antidiabetic, anticancer, and antihypertensive properties, which are closely tied to its antioxidative nature. Given the developing nature of M. palustris utilization in pre-clinical and possibly clinical research, more thorough characterization, pharmacological, and molecular studies should be conducted not only to avoid adverse risks or derogatory interactions with existing drugs, but also to properly direct its use as a nutraceutical agent for specific indications

Key words: *antioxidative, black cincau, flavonoids, natural product, nutraceuticals, phenolic compounds*

INTRODUCTION

South East Asian region has long been well known in using natural resources such as turmeric (*Curcuma longa*) [1], *Aloe vera* [2], and pandan leaves (*Pandanus amaryllifolius*) [3] as traditional remedies for various illnesses owing to its rich biodiversity [4–6]. As another prime example, *Mesona palustris*, colloquially known as 'Black Cincau' in Indonesia and Malaysia, is a local delicacy with noted health benefits. *M. palustris* may be processed to form herbal drinks by boiling fine ground leaves powder or to form edible jelly due to its gelatinous texture and vivid taste. Nevertheless, this plant also has different parts harboring active agents and potential utilities which have yet to be deeply characterized as opposed to other plants in *Mesona* genus.

Various other species within the *Mesona* genus, including *M. procumbens* and *M. chinensis*, have previously been studied extensively. *M. procumbens* extracts have been utilized as a nutraceutical agent. Similar to *M. palustris*, ethanol extracts of *M. procumbens* have recently been observed to pose hypouricemic effects *in vitro* and *in vivo* through modulation of antioxidative xanthine oxidase (XO), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β) [7]. Consumption of *M. procumbens* offers a beneficial potential towards the Chinese population who suffers from increasing prevalence of hyperuricemia [8]. *M. procumbens* extracts have also been observed to provide cytoprotection [9]. The aforementioned effects have been hypothesized to have a correlation with the many reports of its antioxidative properties [10–13]. Such antioxidative effects may be primarily brought about by phenols and other compounds that *M. procumbens* extracts harbor (i.e. protocatechuic acid, *p*-hydroxybenzoic acid, and caffeic acid) [10,11]. Similarly, a third member of the

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Mesona genus, *M. chinensis* is a potential hypoglycemic nutraceutical agent [14] as well as possesses the ability to prevent derogatory protein oxidation and glycation [15], of which are highly related to its antioxidative properties [16,17].

In view of its health benefits as well as many unexplored potentials, this review will then discuss the extraction methods of active natural agents from crude plant sources of *M. palustris* as well as promising pre-clinical potential of *M. palustris* extracts, which focuses on its application as antioxidative, anti-inflammatory, anti-hypertensive, and immunomodulatory agent. Given its abundance and relative ease of plant source processing, *M. palustris* extracts offer an affordable, safe and accessible natural treatment option for surrounding population as a nutraceutical agent. It is of great interest to further characterize the many active compounds present within *M. palustris* and to further study its possible adverse reaction in humans, allergies, or interaction with drugs.

EXTRACTION AND DOWNSTREAM PROCESSING

M. palustris is extractable via various methods which might yield different proportions of active agents. Widyaningsih *et al.* previously described a protocol of obtaining the *M. palustris* powder by macerating and grinding the leaves followed by passing the ground powder through a mesh, and stored at 0-4°C [18,19]. This crude powder could then undergo subsequent extraction protocols, whereby the most conventional option is through water extraction. The crude powder was boiled in 20-times volume of water for 2 h and evaporated at 40°C with the aid of a rotary vacuum-evaporator, followed by freeze drying of the extract [18,19], resulting in pure extracts amounting up to 45% yield [19] with a total phenolic content of 170.33 mg/g [20]. Amongst such phenols in *M. palustris*, alkaloids, flavonoids, and tannins were found to predominate in phytochemical studies [21]. It was also demonstrated that the high antioxidative property was due to the caffeic acid content, amongst other phenols possessing antioxidative properties within *M. palustris* extract [18]. The crude powder could then be subjected to an appropriate volume of ethyl acetate or ethanol for 24 h followed by filtration and evaporation in vacuum for drying.

Conservatively, extracts obtained from natural sources would contain ample unwanted impurities and it is important for downstream processing that active agents yielded are well characterized and purified. Some attempts including the use of liquid/liquid extraction with dichloromethane (DCM), which have shown to improve yield [22] and remove non-polar compounds from the extract [23], although producing lower antioxidative properties in some cases [23]. Related organic solvents such as n-hexane has shown to yield minimal extracts of *M. palustris* with little to no antioxidative properties [21].

Previously discussed solvent-based methods are not only aimed to obtain the extract containing active agents but also to form edible products. Kartikaningrum *et al.* subjected dried *M. palustris* extract mixed with starch to alkaline solvents (i.e. sodium hydroxide (NaOH), magnesium hydroxide [$Mg(OH)_2$] and calcium hydroxide [$Ca(OH)_2$]) to form edible jellies for breaking strength and elasticity analyses [24]. pH also plays a role with regards to gelling properties of edible *M. palustris* nutraceuticals, whereby a pH value of 10 was observed to yield the best gelling property upon mixture with starch sources such as tapioca [25]. Aside from edible jelly production, various other protocols exist to transform *M. palustris* to herbal drinks [26].

Overall, current extraction methods of *M. palustris* are in line with those utilized for *M. procumbens* [27], *M. chinensis* [15,16], or other herbaceous plants [28]. With increasing interest in studying *M. palustris* as a potential nutraceutical agent, more thorough studies which delve into optimization of active agents should be carried out by integrating chromatographic and non-chromatographic analyses, including high performing liquid chromatography (HPLC) and Fourier-transform infrared spectroscopy (FITR) respectively [16,28]. The abundance and relative ease of processing make *M. palustris* extracts an intriguing option for nutraceuticals, which is not only accessible but also affordable.

PRE-CLINICAL APPLICATIONS

Antioxidative Activity

Fulfilling its natural role as a phytochemical, the obvious beneficial effects brought about by *M. palustris* would be its antioxidative properties, which may be quantified and analyzed by assays such as 2,2-diphenyl-1-picrylhydrazyl (DPPH) [21,29–31]. Studies showed that water extracts of *M. palustris* were found to possess oxidative inhibitory concentration 50 (IC_{50}) values at a fairly large range between 30-75 ppm [29,30]. A study utilizing three different Mesona varieties, namely *M. palustris, Cyclea barbata* and *Premna parasitica* reported that *M. palustris* is capable in inducing the strongest antioxidative extract via DPPH analysis with an IC_{50} of 35.99 ppm and 32.59 ppm for ethyl acetate and ethanol extracts, respectively

[21]. Gel microemulsion preparation for ethanol extracts of *M. palustris* was also created to assess its biovailability in drug delivery system, whereby its antioxidative IC_{50} was observed at 70.63 μg/mL [32]. This study conducted by Tamboto *et al.* which utilized a progressive pharmacological concept [32] also considered several concerns, such as first-pass metabolism[33,34]. Biovailability of ingested drugs or nutraceuticals may vary significantly and this might skew results obtained *in vivo* when applied in clinical settings, although techniques such as microemulsion [32,35] and nanoparticle formulations [36] may be applied to counter such problems. Aside from the potential methods to overcome pharmacological concerns, it is also important to understand the molecular mechanisms of *M. palustris* as an antioxidant. Antioxidative effects of *M. palustris* have been reported to be able to activate the upstream transcriptional factors such as Nrf2 [37].

Antidiabetic Activity

Plants of the genus *Mesona* have been traditionally yet infamously consumed by South East Asian and Chinese locals to treat diabetes. Recently, studies were conducted *in vivo* to assess anti-diabetic effects of *M. palustris* extracts with promising pre-clinical findings. Zahra *et al.* utilized oral treatments of glibenclamide (0.09 mg/200 mg) with either *M. palustris* extracts (54 mg/200 mg) or placebo on streptozotocin (STZ)-induced diabetic rat models, whereby β cell count within the pancreas of treated group was significantly higher ($p \leq 0.001$) as compared to the untreated group after treatment duration of 28 days [38]. Anti-diabetic effects within the study was also confirmed by assessing the fasting blood glucose of *M. palustris* extract-treated group (0.795 g/L), which was significantly reduced as compared to the untreated group (1.91 g/L) [38].

An *in vivo* study utilizing diabetes mellitus induced by alloxan (DMIA) rat models was carried out with effervescent powder treatment containing extracts of *M. palustris, P. amyrillifolius, Alpinia purpurata,* citrate acid, tartrate acid, and stevia mixed in carbonated acid granulation [19]. Pathology of β cells within pancreas of treated rats were also found to be rescued as opposed to the untreated group, which was concurrent with their hypoglycemic activities. This study highlights the synergism of *M. palustris* as extracts were also found to work concurrently with other antioxidative agents as a combinatorial approach [19], although interactions between the active agents need to be cautiously studied to eliminate any possible adverse effects.

Despite the promising findings, further studies to deduce the molecular mechanims of active agents in *M. palustris* extracts have yet to be done. Given its natural product nature, it is possible that the antioxidative properties contribute majorly to the protection of β cells from destruction [39,40] or in some cases, enhancement of pancreatic functions [41], which were shown in other anti-diabetic phytochemical studies. Other studies point to the hypoglycemic or insulinomimetic properties of existing compounds that are naturally derived from plants such as *Ficus bengalensis* and *Lepechinia caulescens* [42]. Probable mechanisms of actions of *M. palustris* extracts in combating diabetes may include activation of adenosine monophosphate activated protein kinase (AMPK) [43] and peroxisome proliferator-activated receptor gamma (PPAR-γ) [44]. The many existing molecular data of phytochemicals exerting anti-diabetic properties thus call for attention for more thorough genomic and proteomic studies with regards to *M. palustris.*

Anticancer and Immunomodulatory Activity

Antioxidants have been studied and observed to have close ties with activation of beneficial immune cells and cascades [45,46]. Within *in vivo* models of cancer induced by benzo(a)pyrene, pre-treatment of varying dosages of *M. palustris* water extracts resulted in promising findings, whereby extracts at 1000 mg/kg were observed to reduce cancer incidence by 57% and induced an increase in the natural killer (NK)-stimulating interferon γ (IFN-γ) as well as cytotoxic T cells ($CD8^+$) as compared to the positive control group treated with cyclophosphamide [47]. This finding was also supported by a preliminary study that utilized *Salmonella typhimurium*-induced Balb mice as an immunogenic model and observed the significant increase ($p<0.05$) of IFN-γ, macrophages, $CD8^+$ and NK cells upon treatment with instant tea powder concocted from *M. palustris*, *P. amaryllifolius,* and *Cinnamomum verum* [20,48]. *In vitro* anticancer effects of *M. palustris* were also shown in HeLa cells, whereby water extracts yielded the lowest IC_{50} at 132.6 μg/mL [18]. The anticancer activity described most likely has close ties with the previously elaborated immunomodulatory property of *M. palustris* extracts.

Antihypertensive Activity and Cholesterol Control

Hypertension is another condition whereby *M. palustris* has been traditionally indicated for, much like other more renowned herbs and plants with antihypertensive properties [49–51]. Out of the many enzymatic reactions involved in regulation of blood

pressure, angiotensin-I converting enzyme (ACE) is one of the key players in promoting hypertension through its enzymatic product, angiotensin II [52]. In screening the Indonesian medicinal plants that can inhibit ACE activity, Muthia *et al.* found that *M. palustris* extract at 100 ppm concentration could induce a decent 36.25% of ACE inhibition [53]. Although this effect was not as high as the hypertension drug (captopril) that used as positive control, this study showed that *M. palustris* has the ability to elicit anti-hypertensive effects, although it might not be its primary suitability. Similarly, *in vivo* studies revealed that *M. procumbens* extracts displayed the anti-hypertensive effects by increasing the mRNA expressions of hepatic antioxidant enzymes [54].

Another cardiovascular risk factor to hypertension is the build-up of cholesterol plaques in the inner linings of blood vessels and circulating low density lipoproteins (LDL) or very low density lipoprotein (VLDL) [55]. Thus, induction of hypocholesterolemia in hypercholesterolemic models would help in promoting healthier range of blood pressure as well as circulation of high density lipoprotein (HDL). As observed in *in vivo* studies, instant tea formulation concocted from *M. palustris*, *P. amaryllifolius*, and *Cinnamomum verum* showed hypocholesterolemic effects [56]. After 28 days of treatment at 0.126 g/200 g of Wistar mice weight, the instant tea was observed to significantly reduce cholesterol levels by 50.01% ($p<0.05$) accompanied by increase in HDL by 36.47% [56]. In combination, these 2 effects may provide protective effects to one's cardiovascular health.

Hepatoprotective Activity

M. palustris extracts were also reported to possess organoprotective properties as discussed previously in its relation to anti-diabetic and pancreatic-protective activities [19,38]. Supplementation of *M. palustris* extracts to *in vivo* Wistar rat models, which were dampened with ethanol stress induction for 2 weeks was reported to be capable of rescuing the production of antioxidative superoxide dismutase (SOD) and malondialdehyde (MDA) [30]. The liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which are commonly found to leak out in the events of liver damage were also inhibited upon the treatment, in which treatment of 135 mg/kg of *M. palustris* supplement was observed to produce a significantly lower liver damage of 37.05% [30].

Another study with significant trends of hepatoprotection ($p<0.05$) was also carried out via assessment of ALT, AST, and alkaline phosphatase (ALP), upon treatment with 500 mg/kg and 1000 mg/kg of ethanol extracts of *M. palustris* [57]. The reduced expression of both ALT and AST has also been reported in inducing hepatoprotection in other studies, whereby other markers of liver damage such as lactate dehydrogenase (LDH) [58] may be taken into consideration to build a more robust conclusion.

Antidiarrhea Activity

M. palustris extracts have also been reported to be a potential remedy for diarrhea. Its anti-diarrhea activity was elaborated through assessment of stool consistency and diarrhea occurrences within *in vivo* mice models of diarrhea induced by ingestion of *Oleum ricini*. Mice from treatment groups treated with jelly drinks containing 80 mg/20 g and 160 mg/20 g of *M. palustris* extracts experienced not only lower duration of loose stool production but also better consistency and lower weight of feces produced. All these findings point to strong anti-diarrhea effects comparable to the diarrhea medication, loperamide [59]. Nevertheless, despite its practicality as a remedy for a common health problem, *M. palustris* mechanisms in inducing anti-diarrhea properties have yet to be properly elucidated.

Table 1: Summary of bioactivities of *Mesona palustris*

Bioactivities	Study Design	Treatment Form	Findings	References
Antioxidative	DPPH analysis	Ethyl acetate and ethanol extracts of *M. palustris*	• IC_{50} of ethyl acetate extract is 35.99 ppm. • IC_{50} of ethanol extract is 32.59 ppm.	Farida and Vanoria [21]
	DPPH analysis	Gel microemulsion formulation of *M. palustris*	• IC_{50} of microemulsion is 70.63 μg/mL.	Tamboto *et al.* [32]
Antidiabetic	*In vivo*	Glibenclamide and *M. palustris* extracts	• Significant reduction of blood glucose level. • Significantly higher pancreatic β cell count.	Zahra *et al.* [38]
	In vivo	Effervescent powder of *M.*	• Rescue of β cell pathology in	Widyaningsih *et*

		palustris, *P. amyrillifolius*, and *A. purpurata*	• treated groups. • Induction of hypoglycemic activities.	*al.* [19]
Anticancer and Immunomodulatory	*In vitro*	Water extracts of *M. palustris*	• IC_{50} of HeLa cytotoxicity is 132.6 µg/mL.	Widyaningsih [18]
	In vivo	Water extracts of *M. palustris*	• Reduction of cancer incidence by 57%. • Increase in IFN-γ, $CD8^+$, and NK cells.	Widyaningish *et al.* [47]
	In vivo	Instant tea powder of *M. palustris*, *P. amaryllifolius*, and *C. verum*	• Increase in IFN-γ, macrophages, $CD8^+$, and NK cells	Widyaningsih *et al.* [48]
Antihypertensive and Cholesterol Control	ACE analysis	Ethanol extracts of *M. palustris*	• Induced 36.25% inhibition of ACE at 100 ppm concentration.	Muthia *et al.* [53]
	In vivo	Instant tea powder of *M. palustris*, *P. amaryllifolius*, and *C. verum*	• Cholesterol level reduction by 50.01%. • HDL level increase by 36.47%.	Widyaningsih [56]
Hepatoprotective	*In vivo*	Supplement derived from *M. palustris*	• Rescued SOD and MDA • Inhibition of ALT and AST levels. • Significantly reduced liver damage.	Widyaningsih and Sari [30]
	In vivo	Supplement derived from *M. palustris*	• Significant promotion of hepatoprotection. • Reduced ALT and AST levels.	Widyaningsih and Adilaras [57]
Antidiarrhea	*In vivo*	Jelly drinks derived from *M. palustris*	• Lower duration of loose stool production. • Better consistency and feces weight in shorter duration comparable to loperamide.	Widyaningsih and Safitri [59]

CONCLUDING REMARKS

M. palustris is widely abundant and has been traditionally used as natural remedies to treat various illnesses and medical conditions. These traditional applications have seen new light in the wake of a more robust set of technology and analytical techniques, which allows a handful of studies to be performed and to validate the beneficial effects of this plant species. Based on literature being discussed within this review, it can be concluded that *M. palustris,* alongside members of the *Mesona* genus hold untapped potential as nutraceutical agents which are available, affordable, and effective. These effects include extensive antioxidative properties with evident, albeit potential, utilities in combating diabetes, cancer, hypertension, liver diseases, and diarrhea. Given the apparent safety of *M. palustris* having been utilized throughout the years to assess adverse reactions and effectiveness of the active agents within the human physiology, future studies are highly recommended, especially within the clinical settings. Apart from that, identification and molecular characterization of *M. palustris* active compounds should also be elucidated to provide better insight on its ability in oral applications as well as scale-up production.

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