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REVIEW ARTICLE

Can Medicinal Properties of Watercress be Relevant to Human Health? A Systematic Review Based on Preclinical Study *In vivo*

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ABSTRACT

Nasturtium officinale (Watercress) is a perennial dicotyledonous herbaceous plant and a member of the *Brassicaceae* family. The leaves of this plant are used as a home remedy as expectorant and hypoglycemic. They can also be used in the treatment of hyperlipidemia, hypertension, as well as many other chronic diseases. This finding supports the idea of watercress being a health promoter. In addition, this study intends to provide recommendations for future research. This systematic review was performed by Science Direct, MEDLINE, Cochrane, and Scopus from July 2017 to August 2018. A total of 14 preclinical studies with watercress were selected by the inclusion and exclusion criteria, 13 were with rats and mice and 1 fish. The search terms used were "bioactive compounds," "*Nasturtium*," "preclinical study," and "systematic review." For the quality of the individual studies, we adopted the risk of bias. The results of the selected articles with *Nasturtium* in animals showed positive effects on the improvement of the immune system, hypoglycemic hypercholesterolemia, and anti-inflammatory activity, sex hormones synthesis, the preventive effect on the renal stone formation, and others. Since *Nasturtium* is widely used for therapeutic and nontherapeutic purposes that trigger its significant value, a new approach is necessary. Different combinations and the numerous medicinal properties of its extract juice and leaves, whether administrated orally or topically, demand further studies about other useful and unknown properties of this multipurpose plant. Finally, it is suggested by our reviewers that more studies with animals to be applied to human health, should be investigated of bioactive compounds from watercress.

Key words: Bioactive compounds and systematic review, *in vivo*, *Nasturtium officinale*, preclinical trials, watercress

INTRODUCTION

It is well-established that consumer preference for natural products has resulted in an increased interest in the research, and the use of natural bioactive compounds present in aromatic herbs, spices, fruits, and vegetables that might help to maintain a good health.[1]

Nasturtium officinale R. Br. (*Brassicaceae*), known as a watercress, is a perennial dicotyledonous herb usually found in close proximity to water.[2] It contains a traditional composition of vitamins (A, C, E, and B3) and minerals (manganese, calcium iron, phosphorus, iodine, copper, and fiber). It is also rich in bioactive compounds, named polyphenol and glucosinolate.[3,4] Bioactive compounds are phytochemicals found in plant foods that are capable of modulating metabolic processes and resulting in the promotion of better health.[5]

Phenylethyl isothiocyanate (PEITC), one of the most important bioactive compounds found in *Brassicaceae* family, a chemopreventive agent, which is present in high concentrations as its precursor's glucosinolate. Whenever this vegetable is interrupted, for instance during mastication, the enzyme myrosinase (β-thioglucoside glucohydrolase) is released and induce the conversion of gluconasturtiin into PEITC as well as in the human intestine by microbial myrosinase.[4]

The leaves of this plant, which contains PEITC, are used as a home remedy as depurative, diuretic, expectorant, hypoglycemic, and stimulant. In addition, they can be used in the treatment of stomachic, hypertension, as well as many other chronic diseases and cancer.[6]

Flavonoids are polyphenolic compounds that are abundant in fruits and vegetables, and increasing evidence demonstrates a positive relationship between the consumption of flavonoid-rich foods and disease prevention.[7]

The bioactive compounds found in plants, either combined or individually, have been demonstrated effects as a health promoter. In this review, the watercress supplement has shown flavonoid and glucosinolate in some of its extracts.

The present review aimed to show an overview of the studies that investigated the *N. officinale* supplementation, based on preclinical study, showing the role of watercress through its bioactive compounds. In addition, we intend to identify if watercress can be used as a health promoter.

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METHODS

The protocol for carrying out the study was developed by following the guidelines of Systematic Review Center for Laboratory Animal Experimentation (SYRCLE)[8] and Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[9]

Search strategies

The search was performed at the bases: Science Direct, MEDLINE (PubMed through), SciELO, Lilacs, Cochrane, and Scopus from July 2017 to August 2018. The following search strategy was used for each database. The search terms used were "watercress," "animals," "*in vivo*," "*N. officinale*," *and* "preclinical study." In addition, as a second search strategy, we included studies obtained by manual research in the references of the initially found articles. No search was done for unpublished works or annals of congresses.

Inclusion and exclusion criteria

The inclusion criteria were preestablished as the following:

a. Controlled researches assessing *in vivo* administration of watercress to animals
b. Laboratory animals of any species, age, gender, or models were included
c. Any kind of *N. officinale* or watercress intervention that was compared with placebo control included formulation, dosage, and route of treatment
d. Watercress therapy time was not limited
e. Original data were included independent from other studies.

The exclusion criteria were preestablished as the following:

a. Controlled researches assessing *in vivo* administration of watercress to human
b. Controlled researches assessing *in vitro*
c. Case reports, editorials, abstracts, reviews, and letters or comments
d. Combined with another supplement.

Data extraction and quality of individual studies

Two independent evaluators, according to the methodology, selected the articles and those considered relevant were acquired completely for more careful analysis.

For the quality of the studies individually, we adopted the risk of bias. We accessed the risk of bias of the included basic researches by applying a five-item modified scale according to our previous study.[10] These criteria were as follows: (1) random sequence generation, (2) allocation concealment, (3) incomplete outcome data, (4) selective reporting and (5) statement of a potential conflict of interest [Figure 1]. Each study was given a quality score out of a possible five domains.

SYRCLE's risk of bias tool for animal studies is an adapted version of the Cochrane risk of bias tool, which provides guidelines to score each item. Each domain is evaluated as "yes" (low risk of bias), "no" (high risk of bias), or "unclear" (uncertain risk of bias)[11,12] Cochrane Collaboration's software Review Manager (RevMan 5), current version 5.3.5[13] was applied for data analysis derived a numeric score for the final grade assigned to each study by counting the number of "yes" answers obtained.

RESULTS

The literature search identified 2073 "*N. officinale*" studies; 34 were selected after reading the abstract and only 14 were included after reading the full-text article [Figure 1]. The exclusion of the articles occurred due to the repetition of the research databases or because they did not belong to the inclusion criteria of the studies. We included studies published in English from 2008 to date, with full access, in the form of a preclinical animal test *in vivo,* which evaluated the treatment with watercress in different diseases.

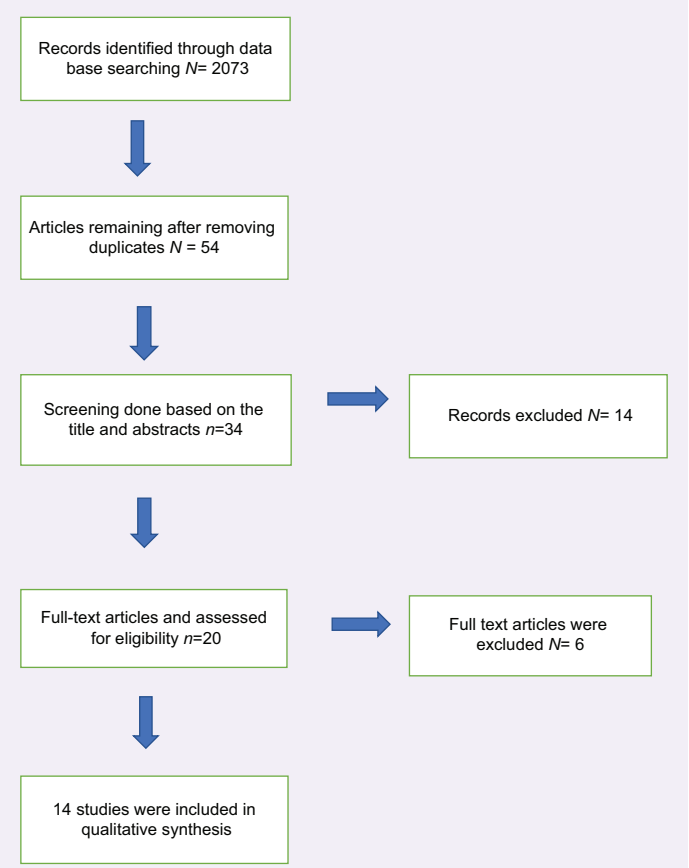

Figure 1: Literary search results in search databases

Study characteristics

Following the exclusion criteria, we analyzed 14 preclinical studies with animals. Among the species, 13 were mice and rats and 1 was fish. Approximately 620 animals were involved, among which 584 were rats and mice of both sexes and 36 were fish.

One of the peculiarities of the cited articles is that watercress presents two main differences; the first is the preparation form (raw food, juices, and extracts), and the second is the chosen dosage intake of that compound. Ten studies supplemented the animals orally and three of them topically; fortunately, all of them showed positive effects, decreasing the symptoms of the diseases chosen in each study, since watercress is recognized for promoting antioxidant activity. The basic characteristics of the 14 studies are shown in Table 1.

The results of the articles selected with *N. officinale* in animals promoted positive effects: In the improvement of the immune system, protective effects, hypoglycemic, hypercholesterolemia, and anti-inflammatory activity.

Risk of bias

For the quality of the individual studies, we adopted the risk of bias with five domains, demonstrated graphically [Figure 2]. For random sequence generation, four of the 14 studies (28.57%) used a random table, whereas the other studies (71.42%) did not report a specific of random sequence generation. For allocation concealment, none of the

Table 1: Basic information of included studies

Studies	Types of studies	Population	Daily dosage	Duration of Intake	Bioactive compounds	Results/ Outcomes
[6]	Control group	18 hypercholesterolemia Rats	500mg/kg/day of *Nasturtium officinale* hydro alcoholic extract single dose- gavage	30 days	Gallic acid Flavonoid (catechin)	Nasturtium has a high hypolipidemic activity
[3]	Control group	18 hypercholesterolemia Rats	500mg/kg/day of *Nasturtium officinale* hydro alcoholic extract (NOE) single dose-gavage	30 days	They said: efforts are going on in our lab to investigate primarily the phytochemical composition of NOE	NOE was anti-hypercholesterolemic and anti- hyperlipidemic
[28]	Control group	Wistar rats divide into several groups of 10-12 in each,	Methanol and aqueous extracts of Nasturtium (10, 50, 100, 200, 400, 600, 800 and 1000 mg/kg) and ethyl acetate extract (5, 10, 50, 100 and 200mg/kg gavage	One week and 8 weeks	They did not report the compound.	At the end of two months' treatment with ethyl acetate extract, the blood glucose level in the group received 100mg/kg of the extract. Only 800 and 1000 mg/kg of the methanol extract of Nasturtium caused a significant decrease in the blood glucose level after a week treatment
[23]	Randomized Control group	36 Fish	0.1 and 1% of watercress extract per 1 Kg	21 days	They did not report the compound.	Increase of globulins in plasma of fish
[17]	Control group	48 male and female Swiss mice	0.5 and 1g/kg weight of watercress juice – gavage	15 days	glucosinolates	These data could contribute to the knowledge of the chemoprevention effects of a diet supplemented with watercress
[2]	Control group	6 adult male Wistar rats and adult male Swiss mice	hydro alcoholic extract of Nasturtium (250, 500 e 750 mg/kg) and topical anti-inflammatory (2 and 5 mg/ear)	A single dose	They did not report the compound.	Anti-inflammatory activity of Nasturtium in systemic and topical application
[15]	Control group	50 Male C57 mice were divided into 10 garoups	Methanol extract of *Nasturtium* doses of 20 mg/kg, 50 mg/kg and 100 mg/kg bodyweight	15 days (sub-acute) and 2 h (acute)	Phenolic and flavonoid	*N. officinale* in high dose can provide considerable hepatoprotection against.6 Gyγ-radiation
[27]	Randomized and control group	4 groups of female winstar rats	100 to 200mg/kg (watercress extract)	4 weeks	They did not report the compound.	Watercress extract at a dose of 200 mg/kg has hypoglycemic and hypolipidemic effects in streptozotocin-diabetic rats
[20]	Randomized and control group	32 Male Sprague Dawley rats	500mg/kg of body weight of hydro-alcoholic extract of *N. officinale*	28 days	They did not report the compound.	The *Nasturtium officinale* extract had a protective effect on arsenic-induced damage of blood cells, could also improve hematological parameters
[14]	Control group	Rats (8 groups of 8 species)	Received daily 50ml of Nasturtium extract-topically	2,7,14 and 21 days respectively	Phenethylglucosinolate Flavonoid Chlorogenic acid	Watercress extract may offer a better therapeutic alternative for patients suffering from mouth ulcers
[21]	Randomized and control group	32 male Wistar rats	750 mg and 1.5 g/kg of hydrophilic extract of Nasturtium-gavage	30 days	They did not report the compound.	Extract in low dose has some preventive effect on renal stone formation

Contd....

Table 1: Contd...

Studies	Types of studies	Population	Daily dosage	Duration of Intake	Bioactive compounds	Results/ Outcomes
[24]	Control group	15 mice tested and 15 mice control	Methanol extract of the aerial parts of watercress (1 mg/mouse) topically applied	20 weeks	Sitosterol-3-O-beta-glucopyrasnoside	Inhibits TPA induced inflammatory ear edema
[19]	Control group	16 male and female Swiss mice	Watercress juice (0,5g and1g/kg body weight) gavage	15 consecutive days	Phenethylglucosinoate Methylsulfinylalkyl Indole glucosinolates and very low level of glucobarbarin	The results support the role of watercress as a diet component with promising proprieties to be used as health promoter or protective agent
[25]	Control group	48 wistar rats and diabetics	Extract of hydroalcoholic Watercress (250 and 500mg/kg)	21 days	They did not report the compound.	Watercress significantly increased sex hormones in diabetic rats

N. officinale=*Nasturtium officinale*, NOE=*Nasturtium officinale* extract

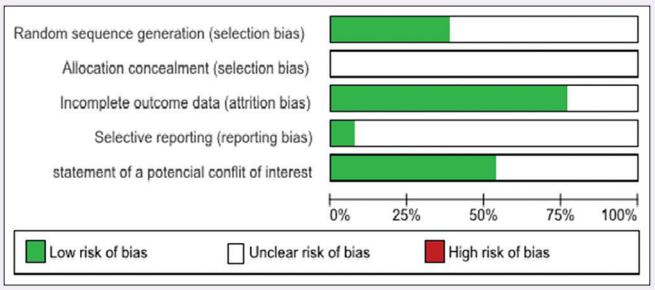

Figure 2: Risk of bias graph

studies reported used opaque envelope method or any other information about concealment. For incomplete outcome data, ten trials reported detailed information (77%). For selective reporting, only one study[20] presented the preclinical trial identifier number, whereas the other trials did not report registration information. For the statement of a potential conflict of interest, eight studies reported positively (57.14%), whereas the others did not write any information about it. The results for the quality of the 14 studies were demonstrated by uncertain or unclear risk of bias (64.3%), low risk (35.7%), and high risk (0%).

DISCUSSION

The family *Brassicaceae* has several types of edible plants, which are rich sources of a variety of nutrients and health-promoting phytochemicals such as vitamins, carotenoids, minerals, glucosinolate, phenolic compound, and flavonoids.[1] Phenolic properties can be used for human health including anti-inflammatory, antimicrobial, antiallergic, and antitumor.[17] Flavonoids are a class of secondary plant phenolic found in fruits and vegetables as well as food products which act as pharmacological active or bioactive compounds in many medicinal plants.[6]

Protective effects

Cruciferous vegetables such as broccoli, cabbage, cauliflower, Brussels sprouts, and watercress, among others, have been extensively studied with regard to their ability to prevent the injuries caused by oxidation in living cells.[25]

Cyclophosphamide (CP) is a bifunctional alkylating agent that is widely used in the treatment of cancer. It is classified as a known human carcinogen based on the extensive evidence found not only in animal studies but also in humans. CP alkylating activity is responsible for its therapeutic activity and its metabolites, such as acrolein, also induce oxidative stress, which leads to deoxyribonucleic acid damage of normal cells and toxicity to various target organs. It was further revealed that watercress juice, as a supplement, reduces the side effects caused by CP. In addition, when supplemented in the CP-treated mice at the end of 15 days, it promoted histological changes.[16] This has probably occurred because of the protective effect found in glucosinolate.[26] In a recent study, the same author exhibited the role of watercress as a dietary component with promising proprieties and showed that it was used as a health promoter or protective agent.[23]

Furthermore, there is also evidence that shows that watercress extract, with its bioactive compounds, protects against arsenic-induced damage of blood cells.[19] A similar extract of *N. officinale* administrated in high dose, increased hepatoprotection against 6 GYγ (gamma)-radiation considerably.[17]

Finally, an extract in low dose (750 mg/kg) of a hydrophilic extract of *N. officinale* has produced some preventive effect on renal stone formation in randomized and control group study with rats.[21]

Immune activity

The immune system is a complex set of physiological mechanisms whose general aim is to defend the organism against nonself bodies, such as pathogens (bacteria, viruses, and parasites) and cancer cells.[27] In this systematic review, in the only study dealing with fish, enhancing immune system activity was demonstrated after 21 days with 1% of watercress extract/kg.[15] Since watercress is rich in Vitamin C, the concentration of hemoglobin in the erythrocyte of fish increased and could improve hematological parameters.[15,19]

Anti-inflammatory activity

It has been reported that phenolic and flavonoid phytochemicals produce strong anti-inflammatory activities.[22] The presence of phenolic and flavonoid constitutes in the crude extract from *N. officinale* has been demonstrated.[3] In the light of the preceding discussion, anti-inflammatory activity of the hydroalcoholic extract from aerial parts of *N. officinale* in oral and topical administration was investigated Its findings indicate potent anti-inflammatory activity of *N. officinale* in systemic and topical application, and propose its potential as an anti-inflammatory agent for the treatment of inflammatory conditions.[2]

In addition, some authors demonstrated that the methanol extract of the aerial parts of watercress (1 mg/mouse), topically applied for 20 weeks, was useful as anti-inflammatory ear edema.[22]

Sex hormone synthesis

According to Mohammadi *et al*., their research showed that the oral administration of watercress hydroalcoholic extract for 21 days in diabetics male rats led to the improvement of rat's fertility as evidenced by a significant increment of sperm cells number and sex hormones.[24] The existence of flavonoids or other bioactive compounds working synergistically in watercress may be the answer of reducing the symptoms of diabetes and improve sperm indexes near to normal.

Hypoglycemic and hypolipidemic effects

It is well-known that a diet rich in vegetables and fruits can reduce cardiovascular disease due to their proprieties. Hyperlipidemia and hyperglycemia are considered as risk factors involved in the development of cardiovascular disease.[28] Therefore, these studies aim to analyses watercress extract; the first study analyzed hydroalcoholic extract of watercress for 30 days after a single dose, and the supplement was able to show cardioprotective effects. The second one proved that 200 mg/kg of watercress extract had hypoglycemic and hypolipidemic effects in streptozotocin-diabetic rat, and the last one demonstrated that *Nasturtium* had a high-hypolipidemic activity.[3,18] According to Hoseini *et al.,* 800 and 1000 mg/kg of methanol extract caused decrease of glucose level in rats.[14]

Mouth ulcer

Medicinal plants are frequently considered less toxic and less side effects than synthetic products. Different population groups have being used extracts of herbs as supporting on the traumatic ulcer healing processing.[20]

It was further revealed, according to that watercress extract used topically on a mouth lesion offers a better therapeutic alternative for patients who suffer from the mouth ulcers, and it was also observed that this solution promoted an increase in fibroblasts, deposition of collagen, contributing in the healing process of the ulcer.[20]

Assessment of risk of bias

According to Hooijmans *et al.,* and Bahramsoltani *et al.,* studies have demonstrated methodological quality score in a different level, the low quality is associated with less precise estimates of the general observed effect size.[12,29] Some authors believe that the components of the score have an important application on the quality of the research.[10] However, modifying five items from the suggestions could be regarded as a criterion for the risk of bias of animal studies for other models.[12] In our review, it was adapted the components such as random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and statement of a potential conflict of interest are widely accepted.[30] We believe in the importance of the study quality when we add the risk of bias in a systematic review, even though the risks sometimes are not appropriate[30] We demonstrated through the risk of bias an unclear or moderate risk according to the 14 chosen trials.

This review focused on the properties of watercress, based on preclinical trials with rats, mice, and fish to be reproduce to human, when it is possible. The 14 studies demonstrated different activities, such as hypoglycemic, hypercholesterolemia, protective effect, sex hormone syntheses, immune system, and anti-inflammatory activity. Despite the differences all of them had shown that the medicinal properties of watercress could be relevant to human health, to corroborate this finding, toxicological evaluation should have been done following the international protocol of subchronic doses,[31] and only one study reported 48 h of acute toxicity with no side effects of different doses of *N. officinale* in Wistar rats treated.[2]

In this systematic review, unfortunately, some limitations have appeared: diversity of methodological approaches observed across studies including animals "characteristics, different outcomes, preparation form, and dosage intake." Hence, the meta-analysis could not be performed accordingly. Despite positive watercress effects showed in the preclinical studies, only six of them demonstrated the bioactive compounds (glucosinolate, phenolic, sitosterol-3-O-beta-glucopyranoside, and flavonoids) responsible for the results, eight studies did not report any compound found in their extract.

These last findings support the importance of conducting more researches on animals which could be applied to human health with low risk of bias,[32] improving the quality of the researches, and also investigating toxicological parameters and bioactive compounds of watercress.

In the light of the above, the need for preclinical studies on watercress for better understanding has been justified to apply to human as a health promoter.

CONCLUSION

Despite the disagreements presented in the studies (sample, methods, results and forms of supplementation, and some studies with no bioactive compounds reported), there is evidence that watercress, in its different forms of administration (oral or topical) and/or intake (raw food, juice, and extracts), has shown positive results with regard to the chosen methodology. The results of this research broaden one's knowledge related to watercress, based on preclinical studies with laboratory animals. The medicinal properties of watercress seem to be relevant to human health when it applies to curative, preventive, or palliative treatment.

Nevertheless, further studies are need with well-designed trials (randomized controlled clinical and preclinical study), low risk of bias and acute and subchronic toxicological evaluation, using international protocols, to ensure the efficacy as well the safety of *N. officinale*, to be applied to human health.

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Conflicts of interest

There are no conflicts of interest.

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