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Effect of Carvacrol Tested on Different *in vivo* and *in vitro* Experimental Studies: Systematic Review

Andressa Coelho Ferreira[1], Cristiano Teixeira Mostarda[1,2,3], Carlos Jose Dias[1,3*], Louryval Coelho Paixao[3], Flavio de Oliveira Pires[1,3], Emydia Rosa do Rego Barros Pires Leal[4] and Marcelo Souza de Andrade[5]

[1]*Department of Cardiovascular Adapatations to Exercise, Universidade Federal do Maranhão, São Luis-MA, Brazil*
[2]*Department of Educação Física, Universidade Federal do Maranhão, São Luis-MA, Brazil*
[3]*Department of Biotecnologia-RENORBIO, Universidade Federal do Maranhão, São Luis-MA, Brazil*
[4]*Department of Ciências Biológicas e Saúde, Departamento de Biologia, Universidade Federal do Maranhão, São Luis-MA, Brazil*
[5]*Department of Ciências Biológicas e Saúde, Departamento de Ciências Fisiológicas, Universidade Federal do Maranhão, São Luis-MA, Brazil*

Abstract

The objective of the study was to show carvacrol isolad in *in vitro* and *in vivo* assays to verify the effects of their dosages on different application areas. The searches were realized in the following databases, pubmed, and academic google using the descriptors carvacrol; carvacrol and *in vitro*; carvacrol and *in vivo*. Thus that in academic google we still use in the advanced search, exclusion of patents and references, as well the inclusion the articles that had the descriptors present in the title. For eligibility, there were 13 articles for analysis. In which, the carvacrol proved to be effective with antimicrobial action, anti-carcinogenic, immune system cell protector, reducer of gastrointestinal lesions, optimizer anti-carcinogenic drug in nanoparticles, as well as mitotic index reducer in bone marrow cells used in high dosages. In conclusion, it is understood that the dosage applied in the right amount can be efficient in the cancer control and elimination of bacteria, in which the carvacrol acts as promising herbal remedy for clinical use.

Keywords: Carvacrol; Dosage; Systematic review

Introduction

Some phytochemicals derived from plants have been very commonly used for the prevention and treatment of different types of diseases due to the belief in their safety from the use in ancient cultures, traditions and societies [1].

The Carvacrol is a monoterpenoid ($C_{10}H_{14}O$) phenolic component extracted of thyme, oregano and marjoram that belongs to a class of phenols that have a ten-carbon unit and are present in the essential oils of many plants (*Origanum vulgare*, Pepperwort, Wild Bergamot, Satureja, *Origanum marjorana*, *Nigella sativa* and Tequila), being recognized as a safe substance by the Food and Drug Administration [2-4].

Carvacrol molecules have been incorporated as useful ingredients in various food products, in the agricultural, pharmaceutical, perfumery, cosmetic, and flavor industries. Besides the use in these types of industries, its biological and pharmaceutical properties have been used in anti-inflammatory, antimicrobial, analgesic, anticancer, and antioxidant processes [2,5].

Thus, in recent decades, the pharmaceutical industry has shown great interest in the research of plants as a source for new structures and for the development of standardized herbal agents with proven effectiveness, safety and quality. This interest is increased for several reasons such as: consumer preferences for natural therapies, high cost and side effects of synthetic drugs and the belief that natural products are innocuous [6].

There are many cases in which natural products exert multiple pharmacological effects, being a practical prerequisite to identify highly effective multi-acting drugs for simultaneous treatment of multifactorial symptoms of chronic diseases [7,8].

Since carvacrol is a substance found in several plants as mentioned above, have as goal to show the effect of carvacrol alone in *in vitro* and *in vivo* tests and their dosages for different application areas.

Methods

The searches were conducted in the following databases, pubmed and academic google using the descriptors "carvacrol; carvacrol and *in vitro*; carvacrol and *in vivo* ". So in academic google we still use in the advanced search to exclude patents and references, as well as include the articles that had the descriptors present in the title and publication period from 1990 to 2017.

We selected the original studies that used animals or animal tissue. Being excluded articles where the carvacrol was in the extract or combined with other substances, dietary intake, vegetable action or microcapsule and review articles.

Results and Discussion

The Figure 1 shows the screening of scientific articles, demonstrate a total of 94 articles found in the search, where 12 articles were included for analysis. A total of 82 articles were excluded because they presented the carvacrol still in the form of extract or still to be used in the protocol associated with other substances, vegetal action, dietary intake and microcapsule.

In the Table 1 we have the approach of two articles with *in vitro* and in *vivo analysis*, showing important aspects such as reduction in colony formation in *Campylobacter* sp infected chickens and reduction of *Echinococcus granulosus* cyst in mice [9,10].

***Corresponding author:** Carlos José Dias, Department of Cardiovascular Adapatations to Exercise, Universidade Federal do Maranhão, São Luis-MA, Brazil, Tel: 65085-580; E-mail: carlosdias.ef@gmail.com

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In the Table 2 we have three large areas related to the approach in the studies, firstly effects with anticancer activity being evidenced in four studies, demonstrating cellular apoptosis and reduction of Bcl-2, reduction of gastric cancer with use of nanoparticles, reduction of intestinal lesions, and genotoxicity in lymphomas. In addition, antimicrobial activity was also found. Finally, effects such as inhibition of dendritic cells as well as protective effect of lymphocytes.

Carvacrol at the non-cytotoxic concentrations for DCs used in the compounds did not decrease the viability of DCs at concentrations up to 10 mg/ml. Therefore, concentrations of 0.1, 1 and 10 mg/ml for and subsequent experiments in DC, at where doses were harmful to both DC and T cells, a decrease in mouse lymphocytes was also obtained in the present study (reducing the proliferation index at doses greater than 10 mg/ml), indicating its immunosuppression [4].

However, the dosage of cravacrol being used and adjusted and balanced can be very efficient as anticancer as presented in some studies.

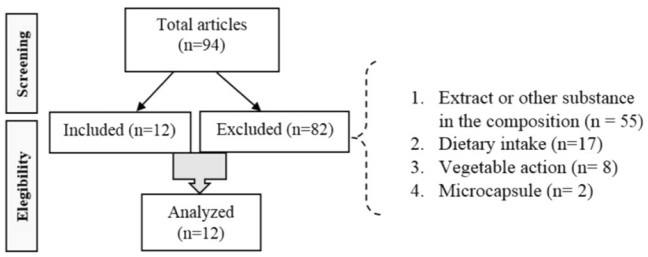

Figure 1: Survey of scientific articles.

The antiproliferative activity and cytotoxicity on human melanoma cancer (A375) cells; its effect on cell cycle control, DNA fragmentation and apoptosis by the cleavage of poly-(ADPribose)-polymerase (PARP) and Bcl-2 gene expression was examined, the same can induce apoptosis by direct activation of the mitochondrial via, which plays a vital role in the anticarcinogen effect [11].

This aspect is also demonstrated in the use of carvacrol by optimizing other drugs to combat gastric cancer by improving the action of nanoparticles [12], as well as in stomach lesions decreasing infections that can progress to cancer [13]. As well as decreased metabolic activity in rat lymphoma with genotoxic action at high doses [14].

In this way the dosages applied in the correct proportions can be very effective in the fight against cancer.

In addition, the studies point to another important antimicrobial action demonstrated in the combat against various types of bacteria such as *Mycoplasma hominis* [15], *Staphylococcus aureus*, *Bacillus cereus* and *Escherichia coli [16]* and *Campylobacter* sp, where this immunoprotective aspect may assist in strengthening the organism against pathological agents, improving, for example, the action of lymphocytes [17].

In Table 3, the *in vivo* approach demonstrated fundamental aspects such as half-life, half-life and depletion of carvacrol, as well as the effect of mitotic index reduction on bone marrow cells.

Important aspects are still fundamental in preclinical research, since carvacrol presents great clinical potential to combat pathologies related of bacteria or disorders of excess cell proliferation, thus

Carvacrol (Dosage)	Study methods	Effects	Reference
120, 200 and 300 mg/kg	Infection of chickens by *Campylobacter* sp.	Delay in formation of *Campylobacter* sp. colonies inducing changes in the intestinal microflora.	[9]
40 mg/kg	Against *Echinococcus granulosus* cyst in mice developed over 4 months.	Reduction of treated cyst weight for 20 days.	[10]

Table 1: Different approaches to carvacrol *in vitro* and *in vivo.*

Carvacrol (Dosage)	Study methods	Effects	
31.21 and 62.5 µg mL^{-1}	Aplication of *Coleus aromaticus*	A375 cells treated with carvacrol for 24 h induced apoptosis by cleavage of PARP and reduction of Bcl-2 gene expression. It can induce apoptosis by direct activation of the mitochondrial pathway, which plays a vital role in the anticancer effect.	[11]
30, 1070 and 120 µg/ml	Activity of human serum albumin (HSA) nanoparticles against gastric cancer.	Carvacrol in combination with chemotherapy agents in HSA nanoparticles can treat cancer cells better than single drug loaded nanoparticles.	[12]
0,20 µg/g	Controled of *Clostridium perfringens* in broilers.	Relief of intestinal lesions in broiler chickens, which may contribute to the control of *C. perfringens* infection in broiler chickens.	[13]
0-2500 mM 700 Mm	Carvacrol *in vitro* genotoxicity test performed in micronucleus (MN) and rat lymphomas assay.	Carvacrol presented small genotoxic effects, but only in the MN test at the highest concentration tested (700 µM) and in the absence of metabolic activation.	[14]
50 and 100 µg/ml	Inhibitory effects of carvacrol on dendritic cells (DCs).	Suppressive effects of carvacrol on DCs on maturation and function, as well as T-cell responses.	[14]
MBC_{90}=600 µg/ml	Antimicrobial effects of five natural substances against 50 clinical isolates of *Mycoplasma hominis.*	The Carvacrol had strong antimicrobial activity and the antimicrobial agent in the treatment of mycoplasmatic infections.	[15]
0,257 mg/ml	*Tratamento contra Staphylococcus aureus, Bacillus cereus Escherichia coli.*	Antimicrobial activity against *Staphylococcus aureus, Bacillus cereus* and *Escherichia coli.*	[16]
5 – 100 mM	Antibiotic growth promoters in the pig nutrition.	Protective effect on lymphocytes, significantly increasing the IC50 to 516 ± 87 IM.	[17]
PARP: Poly-(ADPribose)-Polymerase.			

Table 2: Different approaches to carvacrol *in vitro.*

Carvacrol (Dosage)	Study methods	Effects	Reference
0.001 and 0.0005 μg ml^{-1}, respectively, in plasma and all tissues except for fat both LOQ of 0.01 μg ml^{-1} and a LOD of 0.005 μg ml^{-1}	Topical and intra-mammary product. The levels were measured in plasma, liver, kidney and fat up to 72 h after the last dose.	Semi-life plasma levels were reduced to carvacrol approximately 1.5 h, while wich the estimated half-lives in tissues ranging from 16.9 at 25 h for carvacrol. The predicted amount of time of the molecules found in the body based on the slower depletion time in liver tissue was 10 days for carvacrol.	[18]
30, 50 and 70 mg/kg b.w.	Bone marrow cells from rats.	Decreased of mitotic index.	[19]
LOQ: Lower Limit Of Quantification; LOD: Lower Limit Of Detection			

Table 3: Different approaches to carvacrol *in vivo*.

understanding the half-life and the half-life in the carvacrol [18] is elementary to use effectively in the clinic, as well as the moment of intervention with this phytotherapic, since the same in certain dosages can decrease the cellular division [19], being thus a strong combatant of cells carcinogenic in the early stages.

As study limitations we include the use of only two databases, although they are the most visited and used in the research and no further investigation of the selected studies, such as the statistical analysis study.

Conclusion

Therefore, it is understood that the dosage applied in the right amount can be efficient in the cancer control and elimination of bacteria, using the carvacrol as a promising herbal remedy for clinical use.

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