ATUAÇÃO DO CRAVO DA ÍNDIA (*Syzygium aromaticum*) NA SENSIBILIZAÇÃO DE CÉLULAS NEOPLÁSICAS PARA RADIOTERAPIA: UMA REVISÃO SISTEMÁTICA DE LITERATURA

Action of indian cloves (Syzygium aromaticum) in the sensitization of neoplastic cells for radiotherapy: a systematic review of literature

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Abstract: The search for new molecules that increase the effectiveness of ionizing radiation in the cancer treatment is the subject of several studies. Plant products are excellent sources of discovery and development of new antineoplastic agents. Indian clove has beneficial effects that make it a natural substance potentially suitable for fighting cancer. Thus, the present review was designed to summarize and analyze studies involving the use of clove as a radiosensitizer for neoplastic cells. The systematic review was carried out through a bibliographic research carried out in July 2018 and included relevant studies published so far. The bibliographic search was carried out in specialized databases. A gene search was performed on the GeneCards platform using the keywords "eugenol", "cancer", radiotherapy. These genes were used as input to the STITCH platform, for elaboration of the interaction network. It has been found that studies that address the clove antineoplastic potential are well established in the literature. However, no research studies of this herbal medicine have been found as a radiosensitizer. From the GeneCards 47 genes possibly related to the selected descriptors were extracted. It has been hypothesized that Phyto therapeutic indian clove, more precisely the compound eugenol, can sensitize the neoplastic cells to the radiotherapy through the activating action of the CASP3 and inactivation of CYP1A1. This report highlights the suggestion of the potential of clove as a candidate antineoplastic drug sensitizing neoplastic cells for radiotherapy. However, functional studies should be performed to prove their potential.

Keywords: Cancer; Phytotherapics; Therapeutic efficacy; Essencial Oils.

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Resumo: A busca por novas moléculas que aumentem a eficácia da radiação ionizante no tratamento do câncer é objeto de várias pesquisas. Os produtos derivados de plantas são excelentes fontes de descoberta e desenvolvimento de novos agentes antineoplásicos. O cravo da índia apresenta efeitos benéficos que o tornam uma substância natural potencialmente adequada para o combate ao câncer. Assim, a presente revisão foi delineada para resumir e analisar os estudos envolvendo o uso do cravo da índia como radiossensibilizador de células neoplásicas. A revisão sistemática foi realizada por meio de pesquisa bibliográfica realizada em julho de 2018 e incluiu estudos relevantes publicados até o momento. A busca bibliográfica foi realizada em bases de dados especializadas. Realizou-se uma busca de genes na plataforma GeneCards utilizando as palavras-chave “eugenol”, “cancer”, radiotherapy. Estes genes foram utilizados como entrada na plataforma STITCH, para elaboração da rede de interação. Verificou-se que é bem estabelecido na literatura estudos que abordam o potencial antineoplásico do cravo da índia. No entanto, não foram encontrados estudos de investigação deste fitoterápico como um radiossensibilizador. Do GeneCards extraiu-se 47 genes possivelmente relacionados com os descritores selecionados. Hipotetizou-se que o fitoterápico cravo da índia, mais precisamente o composto eugenol, pode sensibilizar as células neoplásicas para a radioterapia por meio da ação ativadora da CASP3 e inativadora do CYP1A1. Este relato destaca a sugestão do potencial do cravo da índia como candidato a droga antineoplásica sensibilizando células neoplásicas para a radioterapia. Entretanto, estudos funcionais devem ser realizados para comprovação do seu potencial.

Palavras-chave: Câncer; Fitoterápicos; Eficácia terapêutica; Óleos essenciais.

INTRODUCTION

Cancer is a very impactful disease, affecting populations of different social, ethnic and economic characteristics. Although the genetic, epigenetic and pathophysiological mechanisms of cancer have been well described in recent years, cancer has become a public health problem, representing the second leading cause of death in developed countries after heart disease.[1]

The neoplastic cells acquire skills in comparison with the normal cells, in order to maintain their survival and proliferation.[2] In the development of malignant tumors, they can submit proto-oncogenes constitutively active, which predisposes to carcinogenesis, keeping active proliferative pathways of signaling.[3] On the other hand, the expression of tumor suppressor genes is usually decreased and the cell acquires sufficient autonomy to continue multiplying without the need of growth factors. The neoplastic cells also have mechanisms of replicative immortality [4] and greater resistance to cell death mediated by regulation of anti and pro-apoptotic proteins.[5] For maintenance and tumor progression, they stimulate the production of angiogenic factors and modulate cell metabolism to obtain more nutrients.[3, 6]

The radiotherapy (RT) is the therapeutic modality of choice for the treatment of cancer and has played an important role in the control of the neoplastic growth in many patients with this disease, especially when the individual affected by the disease presents no clinical conditions to be submitted to surgery or does not accept the possible mutilations that surgical intervention may entail.[7]

The technical advances achieved in RT have reduced the acute and chronic effects related to therapy.[8] Despite the advances obtained in this modality of treatment, the tumors may have recourse within the irradiated field due to the inefficiency of therapy, leading to a poor prognosis.[9] Therefore, it is crucial to the achievement of research with focus on the development of alternative treatments for increasing the effectiveness of ionizing radiation. A promising approach to increase the effectiveness of radiotherapy in patients with cancer is the discovery and use of drugs that promote the radio sensitivity of neoplastic cells, in order to improve the response rates to RT.

The search for new therapies for the treatment of cancer should seek a balance between the ability of patients to tolerate the side effects of the treatment and the potential toxicity that may occur later.[10] The products derived from plants have excellent sources of discovery and development of new antineoplastic agents since 60 years.

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The first studies on epipodophyllotoxin and its derivatives as cytotoxic agents, and more recently, with the study of vinca alkaloids, vinblastine, vincristine, epipodophyllotoxin and taxanes, which are natural sources of drugs with activity against cancer.[11]

The literature has reported the anticancer potential of aromatic compounds found in foods and plants and there are advanced studies on mechanisms of action and clinical approaches of these compounds.[12-14] *Syzygium aromaticum* L. (indian cloves) are spices which consist of a mixture of phytochemicals, phenolic acids, flavanols glycosides, tannins and volatile oils (phenolic eugenol, acetyl eugenol) with the highest antioxidant activity among plants functional foods .[15, 16] In addition to acting as a powerful antioxidant, the indian cloves also have other beneficial effects, such as: anti-proliferative, anti-inflammatory, antibiotics and antiseptics, which makes this food a natural substance potentially suitable for the cancer chemioprevention.[15]

In the face of all the evidences it was aimed to investigate the potential of indian cloves to increase the effectiveness of radiotherapy in oncologic patients. Thus, the present review was outlined to summarize and analyze the studies involving the use of indian cloves in fighting cancer and products like radiosensitizers to hypothesize the actuation of indian cloves in the sensitization of neoplastic cells to radiotherapy.

METHODOLOGY

Literature search strategy

The systematic review was carried out through a bibliographic research carried out in July 2018 and included relevant studies published so far. This bibliographic search was performed in specialized databases Science Direct (PubMed, Scopus, LILACS, and SciELO) using different combinations of the following keywords: "*Syzygium aromaticum*" and cancer cells, "Sensitization" and "eugenol", "cells sensitization" and "Syzygium aromaticum", radiotherapy and cancer and "Syzygium aromaticum", radiotherapy and cancer and "eugenol", radiotherapy and cancer and "cell sensitization". This systematic review was performed in accordance with the criteria described in items from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[17]

The selection of manuscripts was based on inclusion criteria: pre-clinical

studies (*in vitro* and *in vivo*) and clinical trials involving the use of indian cloves as antineoplastic or radiosensitizers agents of neoplastic cells, as well as pre-clinical studies (*in vitro* and *in vivo*) and trials involving treatments mixing Phyto therapeutic drugs or conventional radiosensitizer drugs and radiotherapy for antitumor therapy. Only articles published in English and containing keywords in the title or abstract were selected. Review Articles, meta-analysis, summaries, conferences, editorials/letters, reports of cases, annals of congress, manuscripts without full text available or articles that did not meet the inclusion criteria were excluded from this systematic review.

For the selection of manuscripts, two independent researchers (authors of this manuscript) first selected the articles in accordance with the title, then with the summary and, finally, through an analysis of the complete article. In cases of non-consensus, a third independent opinion was consulted. The selected articles have been carefully reviewed with the aim to identify and delete items that do not fit the criteria previously established. Additional articles were included in this review after the analysis of all references of the selected articles.

Survey of hypothesis by bioinformatic analysis

In an attempt to predict a mechanism of action by which the indian cloves may sensitize neoplastic cells to radiotherapy a search of genes on platform GeneCards was performed (https://www.genecards.org) using the keywords "eugenol", "cancer", radiotherapy. It was chosen to use the word eugenol due to be a compound widely present in the indian cloves, however, also found in other plants, which would facilitate the discovery of associated genes.

The genes extracted from GeneCards platform were used as input to STITCH platform (http://stitch.embl.de/), with the aim to verify how the chemical compound eugenol interacts with the proteins present on the network of the elaborated interactions. This server provides interactions of chemical compounds with proteins based on known interactions of metabolic pathways, crystalline structures, experiments and drug-target relations. It also allows the use of phenotypic effects, text mining and similarity of chemical structure, in order to predict the relationship among chemicals.

RESULTS AND DISCUSSION

The search of manuscripts held in the database of PUBMED found 27 articles that dealt with the investigation of the therapeutic potential of indian cloves against different types of cancers and 21 articles

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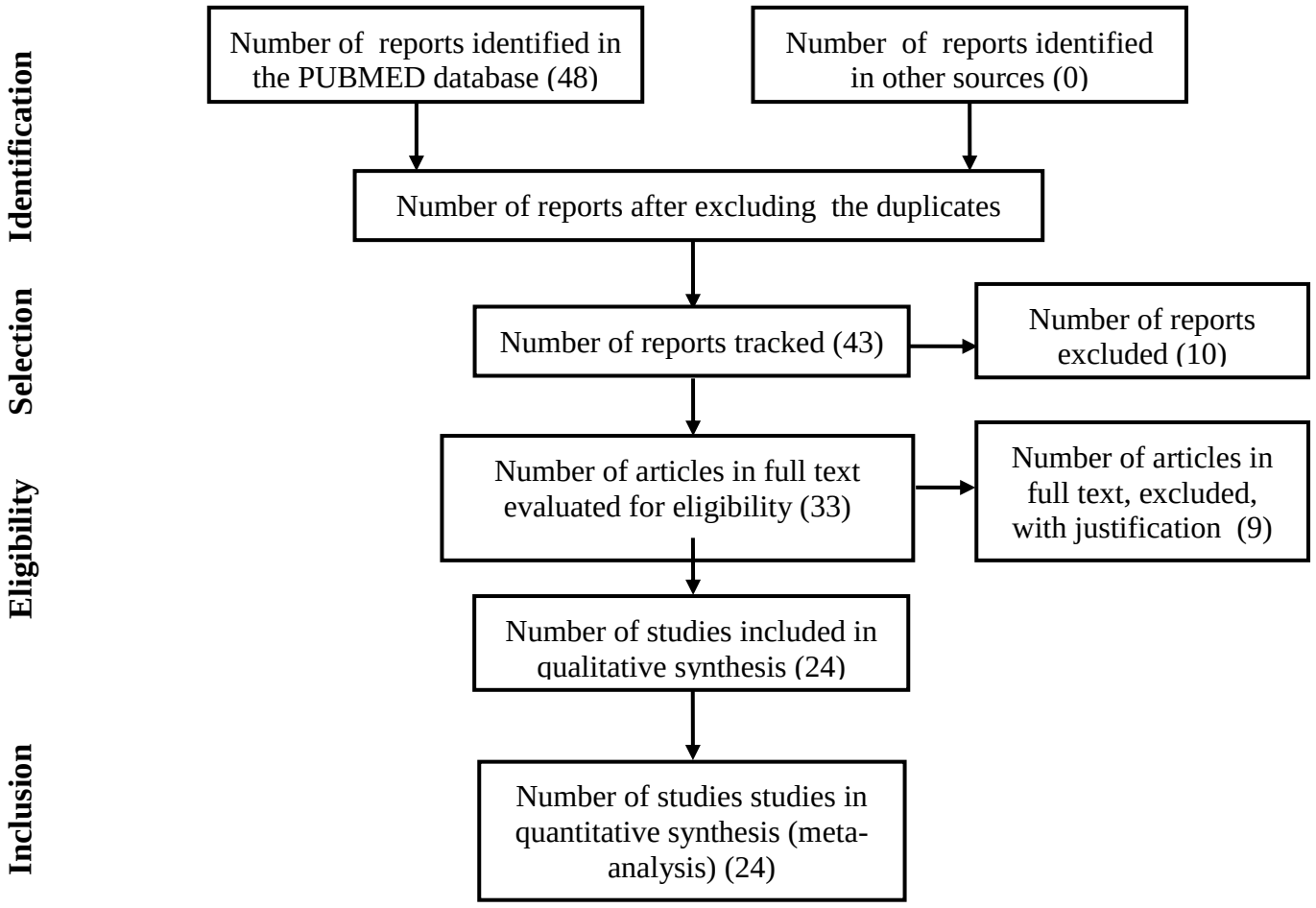
related to the performance of products in the sensitization of neoplastic cells to radiotherapy. However, of this preliminary number, the manuscripts of literature review articles that dealt with the oncologic treatment with indian loves and articles whose origin of eugenol was not the indian cloves were excluded. In addition, articles whose objective was to use the cloves or other compound Phyto therapeutic or chemical as the preventive effects of radiotherapy in the vicinity of the neoplasia were excluded from the search process, as well as the items with a date prior to the decade of 80. Thus, in the search strategy used for the selection of articles the systematic presented in figure 1 was obtained.

Figure 1 - Flow diagram obtained in the articles search strategy



It has been found that studies that address the clove antineoplastic potential are well established in the literature.(Table 1). However, no research studies of this herbal medicine have been found as a radiosensitizer. The absence of articles using the keywords "cells" and "eugenol Sensitization", "cells Sensitization" and "*Syzygium aromaticum*, radiotherapy and cancer " and "*Syzygium aromaticum*", radiotherapy and cancer and "eugenol" showed the scarcity of data in this respect in the pertinent literature, although there are studies addressing other compounds with radiosensitizer potential, as shown in table 2.

The studies that were associated with the "indian cloves and radiotherapy and cancer" performed an approach of this Phyto therapeutic as protector of normal cells, being used, for example, to prevent or minimize the mucositis caused by successive sections of radiotherapy. Therefore, these studies were not included in this systematic review of the literature.

The therapy for cancer patients is based on the use of one or more treatment strategies, including surgical removal of the tumor, radiotherapy, chemotherapy and immunotherapy, phototherapy.[18] Although the radiotherapy is recognized as one of the most effective strategies in the treatment of several types of cancer, the phenomenon of radioresistance[19] has become increasingly frequent, being a limiting factor for the successful treatment of cancer, as it can be observed in some of the studies summarized in table 2.

Table 1 - Summarization of articles found in the search using the keywords "*Syzygium aromaticum*" and cancer

Article (PMID)	Objective	Method	Results/Conclusions of the authors
29318975	Evaluate the antiproliferative activity of essential oils (EOS), within which the indian clove, against some cancer cell lines.	GC-MS Chromatographic analysis Method of self-micro-emulsification and titration method of oil MTT assay and IC50 determinations	Indian clove showed selective activity depending on the type of cell lineage, which may be used as a natural adjuvant to conventional anticancer drugs.
28763204	Investigate the effects of Kumataquenina antineoplastic (extracted from the indian clove).	MTT assay Flow cytometry Western blotting Real Time PCR and ELISA	Kumataquenina presents antineoplastic activities inducing the apoptosis of cells of ovarian cancer and inhibiting the alternative activation

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			of macrophages associated with tumors.
28524540	Evaluate the anticancer effects of indian clove *in vivo* and *in vitro*.	Histopathological and immunohistochemical analysis of mammary carcinomas of mice. Phenotypic and molecular evaluation *in vitro* using MCF-7 cells.	This study showed a significant antineoplastic effect of indian clove on the model of mammary carcinoma *in vivo* and *in vitro*.
28110253	Evaluate the effectiveness of cytotoxicity *in vitro*, of indian clove in nanoparticles of silver, against MCF-7 and HEP -2 cells	MTT assay	Silver biosynthesized nanoparticles showed a significant antineoplastic activity against the MCF-7 and HEP-2 cells.
27702665	Evaluate the cytotoxicity of compounds isolated from the cloves against cells of human ovarian cancer (A2780).	MTT assay	Some of the compounds isolated from the indian cloves showed moderate or weak cytotoxicity in A2780 cells.
27045836	Evaluate the cytotoxicity of compounds isolated from indian cloves against cells of human ovarian cancer (A2780).	MTT assay	Among the isolates, pachypodol (19) proved to be the most powerful cytotoxicity in A2780 cells with an IC50 value of 8.02 μM.
25276075	Evaluate the cytotoxic activity of indian clove to cell lineages of human breast cancer MCF-7.	Test of lethality of brine (BSLT) and test of MTT.	The indian cloves are natural products with excellent cytotoxicity to MCF-7 cells; thus, they are promising sources for the development of antineoplastic agents.
25075040	Evaluate cytotoxic activity of oleanolic acid extracted from the indian cloves.	*In vitro* trials	Fractions of oleanolic acid extracted from the cloves has a potent antineoplastic activity.
25015457	Evaluate the antimutagenic and antioxidant potential of	*In vitro* trials	The results of this study suggest that the indian clove seed can

	extractable components through the indian clove seed.		be exploited as a viable source of bioactive substances for the development of chemotherapy drugs against cancer.
24854101	Investigate the antitumor effects *in vitro* and *in vivo* and the biological mechanisms of the ethyl acetate extract (EAEC) of indian clove.	Western blot and Analysis (qRT) -PCR. The in vivo effect of EAEC and its bioactive component was investigated using the model of xenograft tumor HT-29.	The oleanolic acid (OA) was identified as one of the components of EAEC responsible for its antitumor activity. Both EAEC and OA exhibit cytotoxicity against several cell lineages of human cancer.
22292639	Compare the antineoplastic activity *in vitro* of three different extracts of indian clove.	MTT assay	In the five cell lineages of cancer examined, the extracts showed different patterns of activity inhibition of cell growth, with the extract of oil having maximum cytotoxic activity.
16501250	Evaluate the chemo preventive potential of aqueous infusion of indian clove during carcinogenesis in mice.	Histopathologic and molecular analyzes (*Western blotting*)	The observations indicate the chemo preventive potential of indian clove in view of its apoptogenic and antiproliferative properties.
16235990	Evaluate the chemo preventive potential of aqueous infusion of indian clove during carcinogenesis in *Swiss* mice.	Histopathological analysis in *Swiss* mice.	The results indicate protection against cutaneous papilloma formation in a dose-dependent manner. Observations suggest a promising role for indian clove in restriction of the carcinogenesis process.

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Table 2 - Summarization of articles found in the search using the keywords radiotherapy and cancer aromaticum and "cell sensitization"

Article (PMID)	Objective	Method	Results/Conclusions of the authors
29970481	Explore the radio sensitization mechanisms of BMN673, aiming to combine it with radiotherapy (RT).	Clonogenic assay Chromosomal translocation assay	Observations indicate the path to clinical assays that exploit benefits inherent in the combination of the BMN673 with RT to treat various forms of cancer.
27108384	Evaluate the MI-219 to raise awareness of prostate cancer cells to radiotherapy and androgen deprivation therapy	It was evaluated *in vitro* and *in vivo* with mice xenograft models.	The findings support the therapy with inhibitors of small molecules MDM2 as a strategy of intensification of therapy to improve clinical outcomes in high risk located prostate cancer.
26655813	Assess whether the CREB inhibition increases the sensitization of tumor cells to the cytotoxic stress induced by irradiation-y	Colony formation on agar Western blotting	CREB protects the tumor cells of irradiation γ, and the combination of CREB inhibition plus ionizing radiation will be a promising radiotherapeutic approach.
25079333	Verify if the focal adhesion kinase (FAK; also known as PTK2) in endothelial cells is sufficient to induce sensitization of tumor cells to therapies that damage the DNA.	*in vivo* and *in vitro* assays.	The deletion of FAK in endothelial cells induces increased apoptosis and decreased proliferation within the perivascular compartments of tumor cells of mice treated with doxorubicin and radiation therapy.
18519784	Assess whether the expression of the retinoblastoma transgene 94 (Ad-RB94) increases the effectiveness of radiation therapy (XRT) of squamous cell carcinoma of the head and neck human (HNSCC).	Cell lines HNSCC (JHU006 and JHU012) treated in vitro and in a mouse xenograft model with Ad-RB94.	The treatment with Ad-RB94 increases the effectiveness of XRT through the sensitization of tumor cells.

16203801	Analyze different mechanisms that may be behind the potential synergy between chemotherapy (paclitaxel or doxorubicin) and radioimmunotherapy with alpha radionuclides.	Clonogenic assay of survival. The modifications of the cell cycle were assessed by staining with propidium iodide.	The rate of increase of radiation showed that paclitaxel and doxorubicin were synergistic with alpha radioimmunotherapy.
15175873	Test the effectiveness of the hypoxic cell sensitizer, isometronidazol (ISO), during the irradiation fractioned in two human squamous cell carcinomas.	Single-dose irradiation (SD) under environmental conditions and after 30 fractions in 6 weeks (30 f/6 W).	ISO at a concentration of 750 mg/kg b.w. shows an effectiveness as a sensitizer of hypoxic cells in hypoxic seriously FaDu tumors, but not in less hypoxic GL tumors.
8600096	Evaluate the potentiation of radiation in patients with advanced cancer of the head and neck treated with AK-2123 (Senazole).	Unresectable oropharyngeal cancers histologically proven in stages T3-4, NO-3 and M0	AK-2123 (Senazole), when administered with radiation showed a significant potentiation, which therefore requires further evaluation.
3201385	Evaluate the effectiveness of MTDQ and its derivative soluble in water MTDQ-DA in combination with radiation.	Murine Plasmacytoma X5563 and the lung carcinoma of Lewis were used.	None of the two compounds showed any effect on the response of single-dose radiation, measured by the delay of tumor growth.
3559650	Test the effectiveness of the hypoxic cell sensitizer, misonidazole, in conjunction with intra-operative radiation therapy by electron beam (IORT) and external beam irradiation.	Misonidazole was administered intravenously (IV) in conjunction with IORT from 1,500 to 2,000 cGy to pancreas. Additional external beam radiation administered to 4,960 cGy.	Although there has been a tendency for larger tumors in patients treated with the sensitizer, it was possible to demonstrate an advantage for the misonidazole in this clinical situation.
6432747	Analyze the growth delay of a system of tumor rhabdomyosarcoma of rats with and without misonidazole and subjected to heavy ions radiation.	*In vitro* assays	The hypoxic cell death is increased by higher net bundles of LET and complementarily by the combination of the drug and the LET low portion of the radiation.

The control of tumor growth is variable and depends on some factors, such as the degree of radiosensitivity.[20] In this sense, the radio sensitization represents an alternative to overcome the radio resistance. And it consists in the use of molecules capable of improving the activity of another through the modulation of one or more

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mechanisms of resistance.

The use of drugs or chemical compounds in association with radiotherapy can produce an additive effect on the death of neoplastic cells during the treatment. If the radiotherapy has a great inactivating effect to neoplasia, the association with other compounds may potentiate it.

Several studies have already been conducted comparing different chemical compounds with respect to their ability additive to radiotherapy.[22.23] These studies reveal that the association of chemical agents is related to acute systemic toxicity. Despite this, the range of good results regarding the treatment of the neoplastic mass is possible.[23]

The big problem is that the chemotherapeutic agents currently employed, basically platinum compounds such as cisplatin, have a high level of systemic damage, which ends up reducing, or even opposing, to the expected success of treatment. Exploring the response of chemotherapeutic agents used in association with ionizing radiation, it has been observed an increase in the effectiveness of the treatment. The so-called radiosensitizers become neoplastic cells more susceptible to damages.[24]

It is well established in the literature that natural products have proved to be more effective than conventional anticancer drugs due to their multi-target potential and low toxicity. Such compounds, such as the indian clove, are already widely known as promising antineoplastic agents (Table 1), but little or nothing is known about his their radiosensitizer potential . Several research groups have investigated the role of natural products in the sensitization of tumor cells, however, regarding the indian cloves, this action still remains unclear.

Due to the scarcity of studies on the radiosensitizer role of the indian clove, it was attempted to predict by analysis bioinformatics a possibility of action of this Phyto therapeutic substance as a radiotherapy potentiator In the survey conducted in GeneCards 47 genes possibly related to the descriptors "eugenol", "cancer" and "radiotherapy" were obtained (Table 1).

Gene	GIFtS	GC id	Score ▼	Gene	GIFtS	GC id	Score ▼
TP53	65	GC17M007661	117.96	SOD2	60	GC06M159669	12.84
CDH1	62	GC16P068737	79.67	FOS	61	GC14P075278	12.59
ESR1	67	GC06P151656	46.52	ABCC2	59	GC10P099782	12.16
AR	63	GC0XP067544	43.26	ALOX5	56	GC10P045338	11.75
IL6	59	GC07P022765	32.62	UGT1A1	58	GC02P233760	11.67
PTGS2	60	GC01M186640	32.32	TRPV1	57	GC17M003565	11.39
PLAU	63	GC10P073909	30.50	CD40	60	GC20P046118	10.86
CASP3	61	GC04M184627	30.06	ALOX12	53	GC17P006998	9.92

Table 1 - Genes extracted from GeneCards platform using the keywords "eugenol" and "cancer" and "radiotherapy".

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ESR2	57	GC14M064084	28.91	MB	53	GC22M035606	9.33	
MMP9	63	GC20P046008	26.51	CD80	51	GC03M119524	9.07	
MAPK1	62	GC22M021754	24.59	ALPP	56	GC02P232378	8.98	
CXCL8	48	GC04P073740	21.64	HMOX1	63	GC22P035380	8.98	
JUN	59	GC01M058780	19.63	PTGS1	58	GC09P122370	8.76	
MAPK8	59	GC10P048306	19.44	CD36	59	GC07P080369	8.44	
MAPK3	59	GC16M030125	18.96	IL18	53	GC11M112143	8.39	
CYP1A1	57	GC15M074719	18.58	CCL5	53	GC17M035871	8.04	
CYCS	57	GC07M025158	17.91	IBSP	48	GC04P087799	6.76	
TYR	57	GC11P089177	17.01	TAC1	51	GC07P097731	5.09	
ICAM1	61	GC19P010270	15.66	POR	59	GC07P075899	5.03	
CAT	61	GC11P034460	15.52	PPARA	55	GC22P046150	4.64	
NOS2	57	GC17M027756	15.28	AIFM1	59	GC0XM130129	4.61	
CCL2	58	GC17P034255	14.16	UGT1A	13	GC02P233586	3.43	
DSPP	47	GC04P087608	14.11	TRPA1	55	GC08M072019	1.58	
SOD1	63	GC21P031659	13.85	-	-	-	-	

In Figure 2 the possibilities of interaction of eugenol with proteins of protein interaction network drawn from the genes obtained from GeneCards are observed.

The use of phytotherapy may represent a promising scenario in the oncological treatment. The therapeutic efficacy would be maintained, while healthy tissues would be preserved, possibly offering promotion of greater well-being for the patient through the reduction of side effects and the weakness after radiotherapy treatment. Therefore, in this article it was hypothesized that the Phyto therapeutic indian clove , more precisely the compound eugenol, may sensitize the neoplastic cells to radiotherapy through the action of activating CASP 3 action and inactivating action of CYP1A1, as observed in the protein interaction network previously elaborated (Figure 2a). The hypothesis raised in this work is summarized in Figure 2B.

Figure 2 - Possibilities of interaction of eugenol with proteins of protein interaction network drawn from the genes obtained from GeneCards.

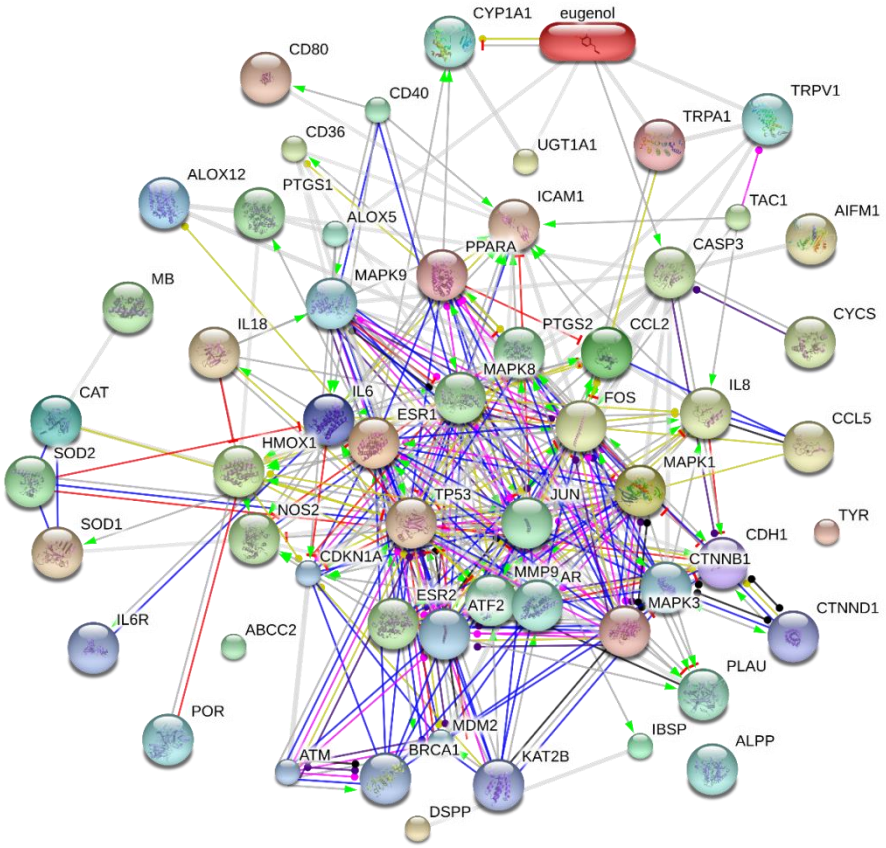
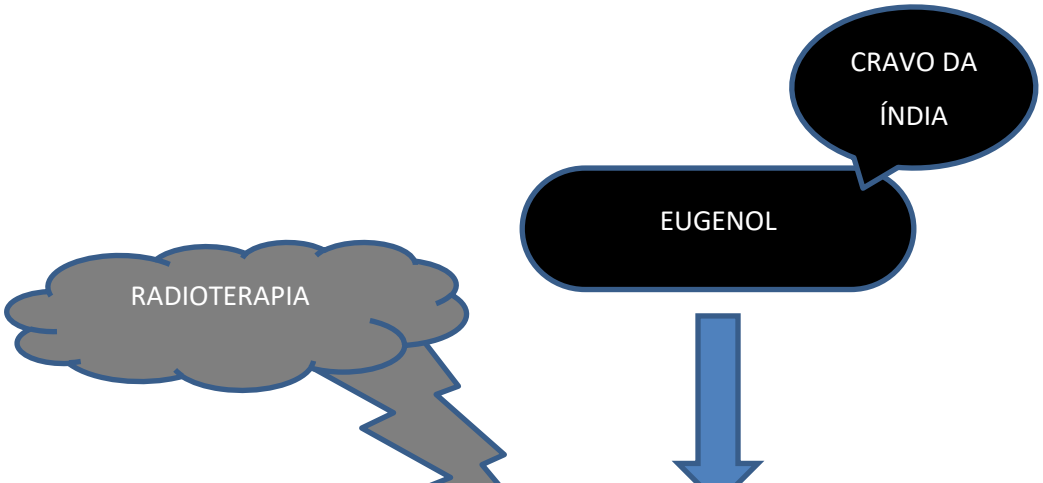


Figure 2b - Hypothesis of the action mechanism of indian clove as the potentiator radiotherapy in oncologic patients.



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The CASPASES are pro-apoptotic molecules. The apoptosis-inducing different signals are detected by the mitochondria, causing an uncoupling of the respiratory chain and consequent release of cytochrome c and activating proteins of apoptosis to the cytosol.[25] When in the cytosol, the cytochrome C forms a complex with APAF1 and CASPASE-9, called APOPTOSSOMO, which promotes the cleavage of the pro-CASPASE-9, releasing the active caspase-9.[26] Once activated, CASPASE-9 activates caspase-3 which will lead to apoptosis.[27]

The CYPs (Cytochromes P450) are enzymes are essential in the development and therapy of cancer, because they act in metabolic activation of several pre-carcinogens and participate in the action or inactivation of antineoplastic drugs.[28] However, the Metabolizing CYPs of xenobiotics differ from the CYPs related to the activation of pre-carcinogens; therefore, the first, derive from polymorphisms among individuals and are more active in the biotransformation; another group of CYPs is not functionally polymorphic, having its principal function in inactivating antineoplastic drugs and activating pre-carcinogens.[28.29]

It is in this sense that the CYP1A1 operates. This enzyme has its activity induced by the receiver of ARILA hydrocarbon (AHR), enabling environmental polycyclic aromatic hydrocarbons and heterocyclic and aromatic amines present in combustion products, such as cigarette smoke. With this, differences in the frequency and intensity of exposure to xenobiotics result in different responses in

the activity of CYP1A1, which may influence certain individuals more susceptible to the risk of lung cancer, for example. [30]

Given the above, it is postulated that the indian clove, by means of eugenol, can promote the destruction of neoplastic cells due to activating CASP3 and inhibiting CYP1A1, making thus, the neoplastic cells sensitive to radiation.

FINAL CONSIDERATIONS

This systematic review summarized information in the literature about the use of indian cloves in the adjuvant treatment of oncological patients, hypothesizing its potential as possible radiosensitizer in cancer therapy. Studies *in vitro* and *in vivo* have shown the efficacy of indian clove as antineoplastic and that some products act synergistically with radiotherapy, increasing its antitumoral effectiveness through several mechanisms, including induction of apoptosis and inhibition of cell proliferation, invasion, metastasis and angiogenesis. This report highlights the suggestion of the potential of clove as a candidate antineoplastic drug sensitizing neoplastic cells for radiotherapy in future studies. Considering that the radio sensitization of neoplastic cells by natural products is a recent strategy and that only a few resources were exploited at the moment, this field of research should expand rapidly over the next few years and therefore deserve to be better studied by means of functional tests.

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