

# Pharmacological Activity of *Calendula officinalis*: A systematic review

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**Abstract**— *Phytotherapy has established a therapeutic medicinal model that has exponentially been increasing over the years. Plants secondary metabolites stand out in the field of pharmacology, as a result of its biological effects in man. This study discusses about the pharmacological effects of Calendula officinalis at different researches, given that this contribution is important among researchers and the entire market, aiming at the therapeutic advancement. Calendula officinalis showed high therapeutic efficacy when applied in healing, anti-inflammatory and antiseptic processes due to its bioactive compounds.*

**Keywords**— *Pharmacological activity, bioactives, Calendula officinalis, phytotherapeutic.*

## I. INTRODUCTION

The tropical forests, located in countries like Brazil for example, are the most diversified biologically source, and this country has a third of the global flora. The development of phytomedicines (PTM) demands a high cost, however, with the sustainable use of the national biodiversity, together with the association between universities and companies, some of the difficulties faced can be supported aiming at generating new PTM to our country<sup>[1;2]</sup>.

Searching for phytotherapy has been verified as a part of health care, since the populations have started asking about the risks of synthetic drugs misuse, associated with its cost, making people replace them with the use of medicinal plants. The PTMs might have their efficacy compared to the drugs produced through a synthetical way, for this, the transformation of a plant have to preserve its chemical characteristics, making that its pharmacological action – observed from the production of secondary metabolites – remain integral<sup>[2]</sup>.

The secondary metabolites, generally, have a complex structure of low molecular weight, they have important biological activities and they are presented at some groups of plants and with reduced concentrations. Before, they were already classified as plant excretion products, however, according to the performed studies, it is possible to realize their participation on biological activities exerted by plants for answering to the environment, as well as, for its notable pharmacological activity, being important not only for the field of pharmacology, but it is

also used in food, perfumery, agronomy, among other things. They can be resumed – in relation to their origin – from the metabolism of glucose mainly through the chiquimic acid and the acetate<sup>[3]</sup>.

The plants secondary metabolites stand out in the field of pharmacology for their biological effects in human. An example of PTM at which the metabolites are extracted is the *calendula officinalis*, where some of their therapeutical recommendation are going to be described during this literary review.

*Calendula officinalis* species belongs to the Asterecae family, common known as marigold, golden flower, daisy or only as calendula. Its name comes from latin calendes, for its great flowering time, being connected to the astrological summer symbol. They have orange petals which are visible during the European and Mediterranean summer. The flowers are the part used for the pharmacological extractions or for another kind of extraction, due to its capacity of producing secondary metabolites which are able to be indicated for therapeutical treatments, such as anti-inflammatory, healings and antiseptics<sup>[4;5]</sup>. Its mainly compounds are the saponins, triterpenoid esters and flavonoid, being also used for burning treatment, skin inflammation, ulcers, wounds and eczema<sup>[4]</sup>.

The study about pharmacological activities of *Calendula officinalis* aims to gather scientific evidences connected to its therapeutical effect of this specie, reaffirming that the continuity of these studies and projects are necessary to authenticate and improve the evaluated

applications. This study still aims at reinforcing phytomedicines using in daily disorders due to the increasing at searching for natural actives, where their use might be assimilated to the synthetical actives, being able to be less hurtful to the organism as used in a safety way and scientifically reasoned.

## II. METHODS

It was performed a systematic review aiming at searching for articles, books, monographs, essays and thesis related to the proposed topic in the following data base online/researching portals as Google Scholar, Scielo (Scientific Electronic Library Online), Scopus, CAPES (Improvement Personal Coordination of Higher Education) and OJS (Open Journal System), through the following descriptors, in English and Portuguese: medicinal plants, phytotherapies, *Calendula officinalis*, bioactives and pharmacological activity. It has been selected researchers published from 2015 to 2020.

## III. RESULTS AND DISCUSSION

Based on Lavagna and others' project which proved that the *Hypericum perforatum* extract provides the surgical healings in childbeds, mainly caesarean operation, Jahdi et al performed a controlled clinical study, randomized for testing the healing effect of calendula in caesarians, since in Iran, the frequency of setbacks after this kind of childbed are high<sup>[6]</sup>. Seventy women aged from 20 to 35, pregnant (from 37 to 42 weeks) were randomly divided in two groups. The group of control did not receive post operative treatment and in the second group have been applied in the seams, twice a day, during ten days, an ointment made by calendula hydroalcoholic extract with two percent of flavonoid.

For pondering the healing degree through the days, it has been adopted REEDA's Scale, which consists of a healing evaluation method in the postpart perineal region and accounts five points of the inflammatory process: redness, edema, bruise, drainage and approach<sup>[7]</sup>. The full numeration for analysis varies between 0 and 15 in which 0 is a skin with healthy features (healthily). For comparing the groups at REEDA's Scale it has been used the T independent test. At the last day of study, 63,9% of the calendula group was at the scale 0-0 and, at this same scale, 0% of the control group. Between 1-5 of REEDA's scale 36,1% from calendula group and 11,1% from control group. Between 6-10, 0% calendula group and 77,8% control group. At the scale between 11-14 there were not

participants treated with calendula, but there were still 11,1% from the group without postpart treatment.

This way, the authors concluded that from the third to ninth post surgical day, the wounds treated with calendula ointment have been completely healed, acknowledging an efficacy in the epithelial reconstructing process, not allowing the releasing of histaminic enzymes which causes inflammation, due to flavonoid, saponins and triterpenoids<sup>[8]</sup>, since the most of calendula elements are stated like eliminators of free radicals and healings through the artificial cross-links producing<sup>[9]</sup>.

A study has performed by Buzzi et al. during thirty weeks has evaluated the effectiveness of the hydrogocolic Plenusdermax® *Calendula officinalis* extract in the healing of stressing ulcers (SU). All patients have been followed by nurses up to the conclusion of the whole procedure. The wounds have been photographed and evaluated according to PUNCH's Scale (Pressure Ulcer Scale for Healing) used for pondering the healing procedure of stressing ulcers and results of treatments, by considering three topics: the area of the wound, the appearance of the wound surface and the amount of present exudate<sup>[10]</sup>.

As higher ulcers demands on more time for healing than ulcers in lower areas, the patients have been divided in two groups, by aiming at getting better results. The whole injured area have been well moistened by spray of calendula, twice a day. The result have reached by Buzzi et al with the topic application of calendula bioactive extract (Plenusdermax®) has been that there was no considerable importance at the healing time of the SU on high and low area. On average, this period has been from  $12,5 \pm 7,8$  weeks. At half the studying time, 63% of SUs have been completely healed. Reaching thirty weeks of treatment, 88% have permanently been recovered, even though, those people who have already had SU for three months.

Plenusdermax® spray showed anti-inflammatory, anti-edematous, anti-erythematous and healing actions, what was actualized through the triterpenoid monoester bioactives, alcohol of triterpene, triterpenic oligoclase and flavonoid<sup>[11]</sup>. The present study, this way, authenticates Jahdi's et al work, for that, both researches attribute the healing activity to the same bioactives. Still on Buzzi's et al study, it was realized bacterioscopy of swabs in the injuries and it was verified the presence of *Staphylococcus aureus*, *Escherichia coli* and others microorganisms, but after the application of calendula spray, it was observed a substantial decreasing of the colonies of these bacterium, verifying an antibacterial and antifungal activity. This result was very important once offensive substances are applied with oxidant effect to cure SU and for

controlling bacterium colonies<sup>[11]</sup>. As a result of this the natural extracts are excellent options to topic alternative treatments.

Carvalho et al also followed a way of ulcering treatment, but on diabetic patient's feet and associating calendula to the laser therapy of low intensity (LTLI). At the first day, the ulcers have been evaluated through clinical attendance, ultrasound and Doppler, at the end (30 days) these analysis have done over<sup>[12]</sup>. The researchers concluded that, the calendula oil, as in the isolated form as combined with the LTLI, showed a distinguishing improvement in the healing and in the chart of pain. Being one more work that contributes with the authors already mentioned, certifying the favour of neovascularization and formation of the collagen fibers to the cellular proliferation, along with the antiseptic and anti-inflammatory effects.

A regulated randomized research, double-blind, performed by Phazohide et al enrolled eighty women with reproductive age and no pregnant for comparing the effect of metronidazole and *Calendula officinalis* in bacterial vaginosis (BV). The ointment of calendula was made of the flower. The entire process of extraction and preparation was realized in the Department of Bacteriology of the University of Medic Sciences Shahid Beheshi, Iran. The bottles and the solidity of the two preparation were similar<sup>[13]</sup>. For diagnosing BV, they used three standards: pH>4.5, whitish discharge or whitish gray or thin; dissipation of fish odor through additioning of 10% of KOH and the presence of pista cell in the microscopy.

When diagnosed, by a randomly way, the women received extracts of calendula or metronidazole<sup>[13]</sup>. Pazhohide et al supported their research on Roosphashire's et al. Evidence that acknowledged an anti-bacterial effect of the *Calendula officinalis* aqueous extract on Gram-positives strains, this way, they confirmed their results when they realized that both groups were free of odor, pruritus<sup>[13]</sup>. Previously, the two participant groups of the study presented symptoms equated to the odor, vaginal discharge, dyspareunia and dysprudia, however, the pruritus was analysed by considerable way in the group that received the *Calendula officinalis*, that is the calendula is as efficient as the metronidazole for actioning against bacterium action. These foundations ensure the observation by Buzzi et al by noting that the bacterium colonies have been reduced after the therapy with Plenusdermax®.

Supporting the following of antibacteriana activity, Ribeiro et al evaluated *in vitro* this pharmacological activity at nine phytotherapeutics mouthwashes available in the market. The calendula showed the higher halo of inhibition of *S. mutans* and activity similar to the

chlorhexidine, as showed in others studies<sup>[14]</sup>. For this, Ribeiro et al proposed *C. officinalis* for controlling the dental biofilm.

As topic treatment, the calendula also was used in injuries caused for the noxiousness of radiation during the operation for combating the cancer. Every care oncological method use aggressive substances to the organism, thus, when it is found a phytotherapeutic that helps in the progress and also can have low noxiousness, this discovery becomes important as for science as for the patient. According to Shneider et al, the goal of comparing the action of *Calendula officinalis* to the essential fatty acids (EFA) in the treatment of radiodermatitis in patients with neck and head cancer. The participants of the survey received randomly bottles with EFA or calendula, both through topic way and with the same bottles. All the skin area was moistened by 12 to 12 hours, with the products would be tested, from first to the last day of radiotherapy. The application was made in the hospital and a familiar was advised how to keep going along at home.

After the fifth and thirtieth day of sessions, the skin was evaluated<sup>[15]</sup>. Both the patients from the group of calendula as the patients from the EFA were receiving radiotherapy relationed to the chemotherapy and there was also a marked amount in the two groups from people who received treatment with Cobalt-60, an gamma radiation emitter, with high tissue permeation and half long life<sup>[16]</sup>. These combination potentialize the radiodermatitis<sup>[15]</sup>. As conclusions, Shneider et al understood that in the EFA group occurred radiodermatitis from the fifth to twentieth session, while calendula's group only occurred it from the twentieth session on. Therefore, calendula had higher protective activity at the appearance of radiodermatitis, secured for its healing acitivity.

Babae et al tested the effect of calendula extract flower in patients with oropharyngeal mucositis (OM), a kind of injury that like the radiodermatitis is caused for the radiotherapy. The individuals were divided in two groups and by eventual way were distributed placebos and mouthwashes with calendula extract, for being used during seven weeks. In the group of calendula, none of the patients needed drugs for the most severe OM, without any cessation of the radiotherapy. Beyond that, at the end of the treatment, in this same group there were not any case of OM during all the treatment. At the second, third and sixth week, the proportion of the injuries were smaller with calendula than with the placebo<sup>[17]</sup>. Such result was relationed to the following secondary metabolites: carotenoids, triterpenes and essential oils and can be applied to Scheider's et al study.

Fontes (2015) has studied on his master degree's thesis the activity of phytotherapeutic formulation with *Calendula officinalis* in the metabolism of rats induced to the dyslipidemia by coffee diet, which consists of a diet with many hyperlipidic food for causing the increasing on the weight of the animals<sup>[18]</sup>.

After the administration of the formulation during forty experiencing days, the author has concluded that the phytotherapeutic made by *Calendula officinalis* 0,42% flavonoids promoted a modulator effect of the lipidic profile, substantially reducing the LDL cholesterol levels and increasing the HDL<sup>[19]</sup>. The dosage 100 mg/kg had the best result in the lipidic rates of rats, this way, Fontes has suggested that this dosage should be used like parameter to the other researches, even though in man. The conclusion was justified with the presence of flavonoids and their antioxidant action and atheroprotective<sup>[19]</sup>, however, the author highlights that it is not possible to verify these properties only to the flavonoids, because others studies have to be performed to verify if these effects are not results of an interaction between a lot of bioactives present in calendula.

More similar to Fonte's study was Kaur's et al research, at which they verified the efficacy of the ethanol extract 95% of calendula flowers after the using of arginine in rats, for the reason that the arginine increases the standards of the mediatory inflammatory and induces the metabolic acidosis, causing the necrotic pancreatitis<sup>[20]</sup>. Based on antioxidant, anti-inflammatory and healing of *Calendula officinalis*, which can be supported through the study by Okzol et al where it was showed that the calendula reduced aminotransferase aspartate, dehydrogenase lactate and phosphokinase creatine, oxidative stress in rats exposed to the cigarette fume and increased the HDL cholesterol rates<sup>[21]</sup>. The present research supported its results at which calendula extract reduced the levels of serum lipase at the third and fourteenth day, beyond that, it assuaged TBARS (levels of reative substances to the thiobarbituric acid) like index of lipids<sup>[22]</sup> and increased the levels of reduced GHS<sup>[20]</sup>.

The upshot of the monography work performed by Martins reinforces Fontes' and Kaur's et al. conclusions. Martins quantified the oxidant activity of each bioactive found in the ethanoic solution of calendula desidratated flowers at different concentration, relationing to the efficiency of the extract. The authors used a method to find the presence of antioxidant compounds, based on elimination of the permanent free radical 1,1 definil- 2 picrilhidrazil (DPPH method)<sup>[23]</sup>, by concluding that calendula antioxidant action is derivated from flavonoids, cartenoids and essencial oils<sup>[24]</sup>.

A list of the works used in this bibliografic review is found in the Table 1, aiming at better exposing the results. In the Fig. 1, as a quantitative way, are showed such pharmacological activities remarked at each study.

Table.1: Abstracts of the works used in the present research

STUDY	YEAR/AUTHOR	CONCLUSION
The impact of calendula ointment on cesarean wound healing: A randomized controlled clinical trial	Jahdi et al (2018)	Calendula oitment efficacy in the caeserians healing process.
Usage of <i>Calendula officinalis</i> in the prevention and treatment of radiodermatitis: a randomized double-blind controlled clinical trial	Schneider et al (2012)	The reduction at the development of radiodermatitis in people who used calendula was greater than those ones who used EFA
Pressure ulcer healing with Plenusdermax® <i>Calendula officinalis</i> L. extract	Buzzi et al (2016)	Promising antibacterial, antifungic and analgesic activities in the <i>Calendula officinalis</i> extract
The effect of <i>Calendula officinalis</i> versus metronidazole on bacterial vaginosis in women: A double-blind randomized controlled trial	Pazhohideh et al (2018)	<i>Calendula officinalis</i> antibacterial activity is as eficiente as metronidazole.
Herbal formulation containing <i>Calendula officinalis</i> effect	Fontes (2015)	Significant improvement at the lipidic profile of the rats, due to the

on lipid metabolism in Wistar rats fed with cafeteria diet		antioxidant properties present in calendula.
Antimicrobial activity of different herbal mouthwashes	Ribeiro et al (2015)	<i>Calendula officinalis</i> showed antiseptic, antibacterial and biostimulant actions.
Efficiency studies and antioxidant activity of calendula extracts by processing extract through solvent	Martins et al (2017)	Comprovação of antioxidant activity actualized through flavonoids and caretonoids.
<i>Calendula officinalis</i> ameliorates l-arginine-induced acute necrotizing pancreatitis in rats	Kaur et al (2016)	<i>Calendula officinalis</i> effect in the increasing of GHS levels and reducing of TBARS levels.
Low-level laser therapy and <i>Calendula officinalis</i> in repairing diabetic foot ulcers	Carvalho et al (2016)	The use of <i>Calendula officinalis</i> oil by isolated way or combined with LTLI provided acceleration in the tissue repair, decrease of the wounded area, anti-inflammatory and analgesic action.
Antioxidant capacity of <i>Calendula officinalis</i> flowers extract and prevention of radiation induced oropharyngeal mucositis in patients with head and neck cancers: a randomized	Babae (2013)	Reduction of the intensity of oropharyngeal mucositis.

controlled clinical study		
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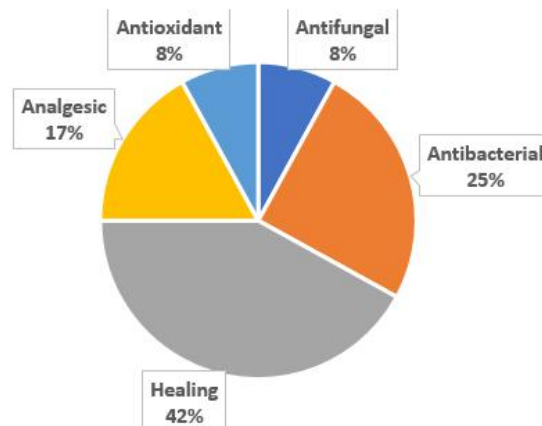


Fig. 1: Pharmacological activities of *C. officinalis* founded in the literature.

#### IV. CONCLUSION

Nowadays, it is verified a greater preoccupation in relation to the alopatics drugs using, as due to their effects as to their cost. The increasing of studies and researches in relation to the phytomedicines is important due to its efficacy, that in some cases, it can be compared to with the synthetic actives. The results observed at this literary review can significantly contribute for the population health improvement, for the evidences showed until this moment, concluding that *Calendula officinalis* using, when applied on healing, anti-inflammatory and analgesic processes, showed higher therapeutic efficacy.

Furthermore, it is important to emphasis the importance and necessity of going on the clinical essays and studies, which gather data that show efficacy and security for phytomedicines using.

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