Prospection technological and cientific: Ferulic Acid Activity on Topical Formulations

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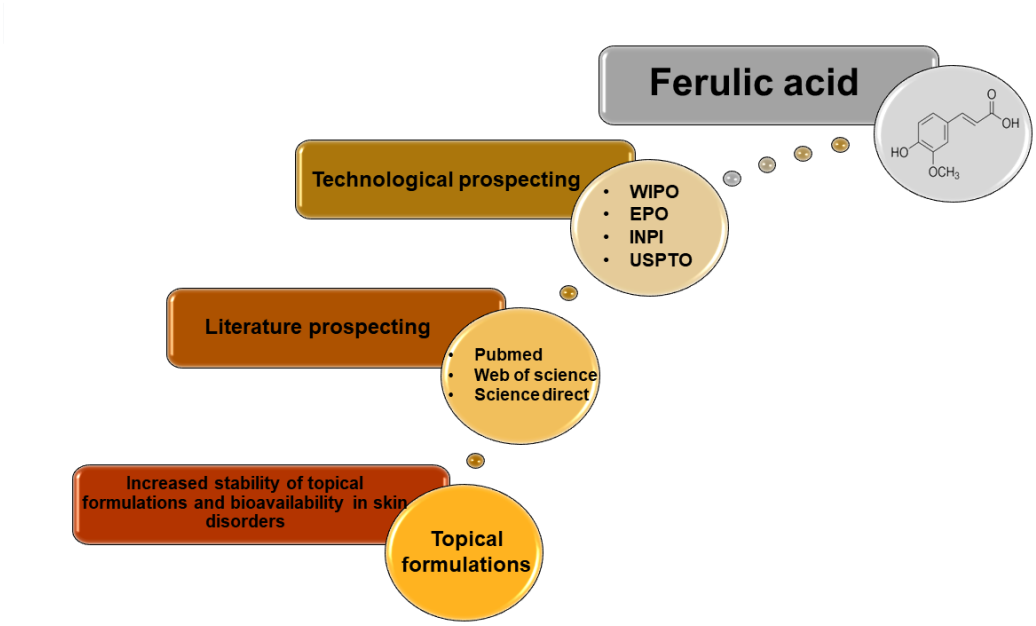
ABSTRACT

Ferulic Acid is a phenolic compound widely found in monocotyledons with a large application field, especially in pharmaceutical and dermo-cosmetic industries. It has proven antioxidant, anti-inflammatory and other activities especially due to its molecular structure. The main factor that can lead to more serious skin damages like inflammation, dryness, wrinkles, and cancer is the exposure to UV radiation increasing the radical oxygen species ratio. The aim of this review is to evaluate the application of Ferulic Acid in topical formulations and the technologies used to enhance its bioavailability and stability in the compositions. This review covers technological publications in the WIPO, EPO, INPI and USPTO databases and scientific publications in the PubMed, Web of Sciences and Science Direct databases, analyzing the trend and application of Ferulic Acid by country and years of publication. Having a bigger picture of its effects by in vivo and in vitro studies specifically in topical formulations. The Ferulic Acid showed great activity in many formulations for topical application and improved stability and bioavailability when combined to new technologies and techniques. Showing an open path to target the treatment of skin disorders.

Keywords: Ferulic Acid; Pharmaceutical; Terapeutic Activity; Topical Application;

GRAPHICAL ABSTRACT



1. Introduction

Phenolic compounds are attractive due to their antioxidant activity [1]. Ferulic acid (3-methoxy-4-hydroxycinnamic acid) is a phenolic compound, occurring in cell walls of seeds and leaves of monocotyledons and can be found in free form or conjugated to other substances like carbohydrate, proteins and fatty acids. This substance has proven results cites in cientific articles in the treatment of various diseases, such as cancer and diabetes [2,3], as well as lipolytic [4], antimicrobial action, anti-inflammatory [5] and, mainly, antioxidant activity [6], responsible for its main benefits and applications [7].

The compound molecular structure and characteristics explain its main activity and interactions, these chemical aspects are: The benzene ring, the side chain, the COOH carboxyl group that protects against lipid peroxidation, the OH hydroxyl substituent that is connected directly to the benzene ring and fights the reactive oxygen species, inducing the resonance and stabilizing the molecule, and the OCH3 methoxyl group that can form hydrogen bonds in the molecule giving more stability. The Ferulic Acid has low water solubility mainly because of the aromatic ring and the carbonic side chain. Although it has polar groups in the structure that can interact by hydrogen bonds with the water molecules, the apolar aspect is predominant, because of the benzene ring and the side chain, making the Ferulic Acid a more apolar compound, less soluble in water. The characteristic leads to low oral bioavailability and makes the development of cosmetic and pharmaceutical compositions more challenging [8, 9,10,11].

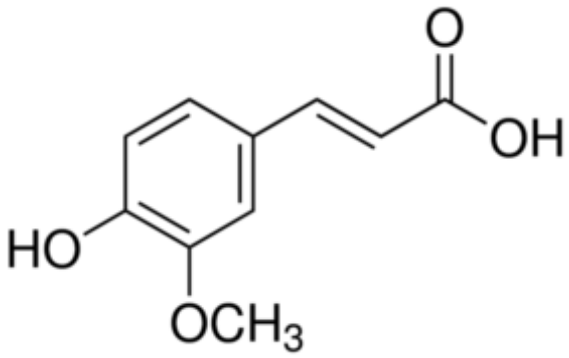


Figure 1. Ferulic Acid molecule from PubChem

Conditions that affect the skin include physical such as ultraviolet rays, infrared rays, air pollution, internal causes, and stress. Among various factors, the skin is damaged by external causes such as ultraviolet rays and infrared rays, thereby causing trouble [11]. Exposure to solar ultraviolet (UV) rays initially causes sunburn, tanning, inflammation including erythema and later premature photoaging with mottled,

darkened pigmentation, wrinkles, dryness, leathery texture, as well as the more serious consequences of immunosuppression, precancerous actinic keratoses and actual skin cancer [7]. It happens mainly by increasing cellular levels of reactive oxygen species (ROS), which damages lipids, proteins, and nucleic acids in both epidermal and dermal cells [12]. Ultraviolet irradiation is a potent generator of oxidative stress in the skin. It has been shown that *in vitro* and *in vivo* that both UVA and UVB spectra lead to Reactive oxygen spicies production, impaired antioxidant defense and thus to oxidative damage [13,14].

Because these consequences are mediated by ROS, delivering antioxidants (isolated or with other components acting synergically in the formulations) directly to the skin should prevent injuries, damages, relief skin irritation and smoothes the complexion aspect [1,15]. Along with the phenolic compound results in the treatment of various diseases and antioxidant activity, Ferulic acid has a wide range of applications on formulations to be explored, from and sèrum, cream and lotion, to oil and ointment compositions depending on the therapeutical target and application [16].

In view of the above, the objective of this research was to conduct a systematic review from the scientific and technological perspective on the use of ferulic acid (FA) in topical formulations. The article was divided into two main sections, comprising literature and technological prospection.

2. Prospecting the literature

A scientific prospection was carried out in databases to understand the state of the art in relation to the use of ferulic acid in topical formulations. The keywords "ferulic acid" "topical formulation" and "ferulic acid" "topical formulation" were used. The searches were carried out between November 2019 and March 2020, and no cut-off dates were established for the articles. The research was conducted at PubMed, Web of Sciences and Science Direct. Initially, the articles were identified in the databases and the abstracts without a complete article available, books, review articles and those not specifically related to the theme in question were eliminated. The duplicate summaries were then deleted. Soon after reading the abstracts, the selected articles were read in full, excluding those with perspective on another outcome.

Based on the research conducted in the databases listed above, 79 articles were found within the criteria. In the initial screening, 46 articles did not meet the inclusion

criteria and were excluded by reading titles and abstracts. Thirteen articles were later deleted because they were duplicated in the analyzed databases and, finally, 16 articles were included. In each selected article, the following information was collected: authors, year of publication, country, application and analyzed activity. The search schema and database values are described in Figure 2.

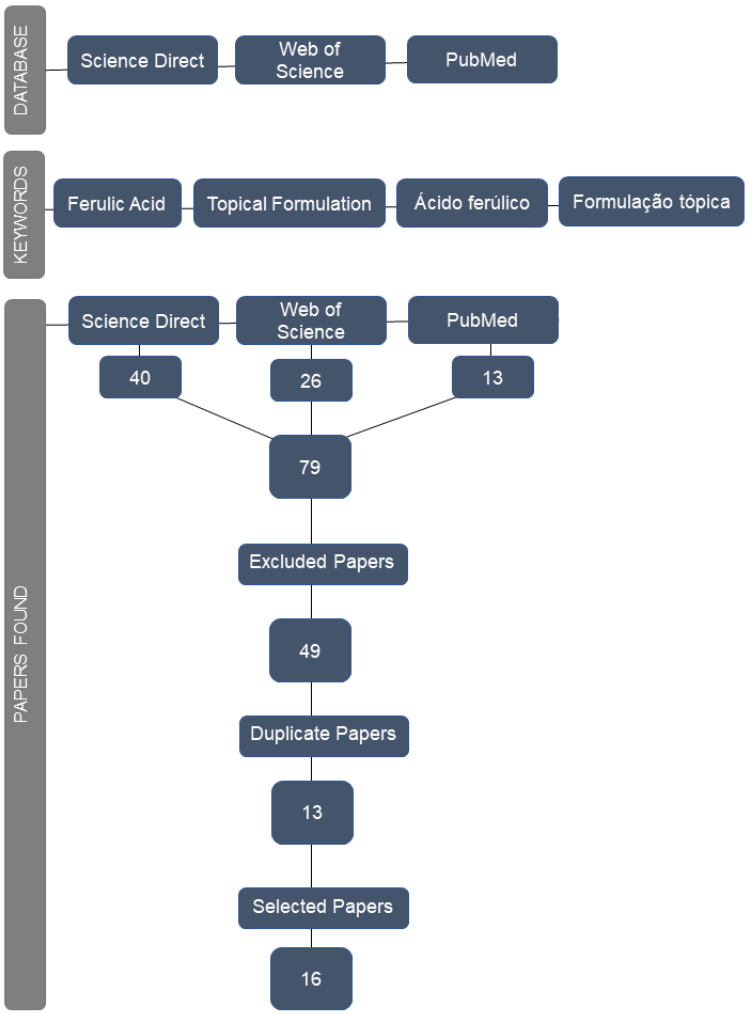


Figure 2 - Search strategy and results found in scientific prospection

Although the first publications on ferulic acid were initiated in 1992, through studies conducted by Graf [17]. Its use in topical formulations began to be significantly explored in the 2000. Saija et.al.[18] evaluated *in vitro* skin permeation and *in vivo* photoprotection of caffeic acid and ferulic acid in aqueous solutions. Throughout the study it was found that caffeic and ferulic acids can be successfully used as topical protection agents against UV-induced skin damage. Ferulic acid showed better skin permeation *in vitro* and both proved significant protection to the skin against UVB-induced erythema.

2.1. Association of ferulic acid with antioxidant vitamins

Some papers have explored the association of ferulic acid with other acid in topical formulations. The pioneering study for this context was conducted by Lin et.al. [19], in an attempt to improve the stability of vitamins C and E in topical formulations, explored the efficacy of several low molecular weight antioxidants that are available in chemically pure form. Chemical stability was determined after 30 days at 45 ° C and found that AF provided stability of more than 90% for L- ascorbic acid (vitamin C) and 100% for α-tocopherol (vitamin E). A concentration of 0.5% gave the best combination of stability and efficacy of the formulation. In addition, its incorporation doubled the photoprotection for skin irradiation and efficiently reduced the formation of thymine dimers and keratinocyte apoptosis. This combination of pure natural antioxidants of low molecular weight provided significant synergistic protection against oxidative stress in the skin and was pointed out as useful for protection against photoaging and skin cancer. The mechanism of the stabilizing effect of ferulic acid on vitamins C and E neste artigo is unknown. Provalvely interact with pro-oxidative intermediates or serve as a sacrificial substrate. It is also possible that their interactions can be improved with the low pH of the formulation. The effect of ferulic acid on photoprotection is probably related to its antioxidant activity [19].

Subsequent to this study Tournas et.al.[20] conducted a comparative study between two formulations. The authors compared a formulation containing ubiquinone, idebenone and kinetin with the formulation proposed by Lin et al. (0.5% ferulic acid, 15% L- ascorbic acid and 1% α-tocopherol). At the end of the study it was found that the formulation containing FA was considerably better for photoprotective effect in UVA and UVB emission tests *in vivo*.

During the search of the databases, it was observed that many researchers invested in studies of topical formulations that contain the association between ferulic acid, vitamin C and E. Murray et. al. [21] determined whether a topical formulation with 15% L-ascorbic acid, 1% α-tocopherol and 0.5% ferulic acid (called CEFer) could protect human skin from substantial amounts of simulated solar UV radiation. CEFer and his vehicle were applied to human skin for 4 consecutive days. Each adhesive was irradiated with simulated solar UV and one day later the skin was evaluated for erythema and burned cells, in addition to immunohistochemically analyzed for thymine and p53 dimers, formation of UV-induced cytokines, including interleukins IL-1a, IL-6, IL-8 and IL-10 and tumor necrosis factor-α. This study demonstrates that this combination of antioxidant

vitamins can be applied topically to the skin and protect against UV-induced oxidative damage. In addition, protection was also provided against DNA mutations that have been shown to be associated with skin cancer. The authors conclude the paper by stating that its mechanism of action is distinct from sunscreens and it is expected that its use is supplemental to provide maximum photoprotection for the skin.

Burns et. al. [22] analyzed the differential effects of topical treatments with ferulic acid, vitamin E and C (CE Ferulic®) on the development of skin tumor induced by ultraviolet B light in Skh-1 mice. The model mimicted women exposed to UVB regularly between childhood and early adulthood, sharply reducing sun exposure and beginning to apply topical antioxidants before any injury was sustained. Thus, therats were exposed to UVB for 10 weeks in order to induce skin damage. Before the appearance of skin lesions, rats were treated for 15 weeks with the topical antioxidant, with no additional exposure. The present study demonstrated that topical treatment C E Ferulic effectively reduced the number and tumorload, preventing the development of malignant tumors in Skh-1 female mice.

Wu et. al. [23] conducted a study to evaluate the efficacy of a topical antioxidant containing 15% L-ascorbic acid, 1% α-tocopherol and 0.5% ferulic acid in protecting the skin against photolesion induced by simulated ultraviolet solar irradiation (ssUVR) in Chinese women. In this study, 12 healthy women were included. Before exposure to UV rays, each formulation (antioxidant and vehicle) was applied for 4 days in demarcated areas on the back. After exposure to UV rays, digital photographs were taken, the color of the skin was measured before and after radiation. Skin biopsies were obtained 24 hours after exposure to ssUVR for immunohistochemistry analysis. Topical use of antioxidant complex reduced clinical signs related to acute photolesion and conferred significant protection against biological events in human skin compared to other irradiated sites without applying the formula.

Waibel et. al. [24] evaluated whether administration of topical formula containing vitamin C, E and ferulic acid in the postoperative period of fractional ablative laser could improve wound healing. Fifteen healthy individuals between 30 and 55 years of age were treated with vitamin C, E serum and ferulic acid within 2 minutes immediately after CO2 fractional laser ablant surgery and daily during the healing process. Patients were evaluated daily for 7 days through photographs, questionnaires and molecular evaluation.

The use of fractional ablative lasers to provide bioactive agents to a patient through channels of predetermined depth in the cutaneous tissue has broad clinical implications. After the skin injury, a set of complex biochemical events happen to repair the damage. It is generally recommended that topical products be avoided during the first week of recovery. However, incorporating a topical product can help in the healing process. The authors found that treatment with these antioxidant acids can block negative regulation induced by bFGF laser treatment (bFGF is a glycoprotein, widely used in the treatment of wounds and ulcers) on the skin. Molecular data analysis revealed that the formulation can protect or stimulate bFGF, which in turn increases fibroblast activity to repair wound damage in the first days after injury and decreases postoperative downtime.

Researchers Kim and Lee [25] addressed the use of topical application of the combined formulation of vitamin C, vitamin E and ferulic acid (CE Ferulic®) as an adjunct after treatment with Nd: YAG (QSNY) lasers of Q-switched in individuals with lentigins and melasma. Thus, a randomized, prospective study was conducted with eighteen men and women between 26 and 53 years of age. The individuals were treated with CE Ferulic® on a random side of the face immediately after the QSNY laser and twice a day for two weeks. Patients were evaluated using digital photography and spectrometry to evaluate melanin index and erythema index. The melasma severity score and overall improvement scores were also evaluated. The side that received the antioxidant solution showed a significantly greater reduction in melanin index. There was no significant difference in post-treatment erythema. The authors conclude the study by confirming that the use of a topical antioxidant immediately after laser treatment is safe and well tolerated, however, further studies are needed to evaluate the long-term clinical effect and mechanisms involved in reducing skin hyperpigmentation.

Oresajo et. al. [26] investigated the use of cloretin (vegetable antioxidant) associated with vitamin C and ferulic acid (CFerPhlor). In this study, the role of UV irradiation in skin damage and its protection by CFerPhlor in humans using erythema, formation of sunburned cells, formation of thymine dimers and other biochemical markers was compared. A 10% l-ascorbic acid solution on a hydroglycic basis (water, butylene glycol, dipropylene glycol and ethanol) containing 0.5% ferulic acid and 2% chlorretin. The solution was adjusted to pH 2.5 to achieve maximum topical absorption. Ten individuals aged between 18 and 60 years were treated with the antioxidant product

in the lumbar region for four consecutive days. On the fifth day, digital images were taken and 4 mm puncture biopsies were collected at both test sites for morphological and immunohistochemical studies. UV irradiation significantly increased human skin erythema, there was also sun burned cells, formation of thymine dimers, expression of the metalloproteinase-9 matrix and expression of p53 protein. All these changes were attenuated by CFerPhlor, so the antioxidant composition blocked these effects. According to the authors, the use of sunscreens for skin photoprotection is well established. However, sunscreens generally do not provide 100% protection against UV radiation due to non-uniform application on the skin surface. As sunscreens and antioxidants work by different mechanisms, they are expected to be complementary.

To finalize this section of use of ferulic acid associated with other antioxidants, Cassano et.al. [27] evaluated a dextran hydrogel containing ferulic portions with vitamin E (α-tocopherol) to improve its topical distribution and also its stability, due to direct exposure to UV light. According to the authors, these hydrogels are capable of increasing the penetration of the drug, improving the pharmacological effects for transdermal administration that have always been challenged by the barrier property of the stratum corneum. Thus, foi studied its ability to inhibit lipid peroxidation in the microsomal membranes of the liver of rats induced *in vitro* by a source of free radicals, which was terc-butyl hydroperoxide. Hydrogel was also characterized by release behavior and deposition in rabbit skin. Vitamin E deposition was compared by hydrogels, respectively, containing and not FA. According to the authors, ferurated hydrogel was a more effective carrier in protecting vitamin E from photodegradation than hydrogel without antioxidant portions and so they indicate that antioxidant hydrogel maybe of potential use for cosmetic and pharmaceutical purposes as a vitamin E transporter.

2.2. Association of ferulic acid other substances

Trombino et. al. [28] reported the synthesis of ferulic portions cellulose hydrogel and the evaluation of its antioxidant and eliminating activity. The hydrogels were obtained through radical copolymerization of acrylcellulose (AcrC) with N-dimethylelacamide (DMAA). Its antioxidant activity was evaluated using two tests *in vitro:* inhibition of lipid peroxidation in microsomal membranes of rat liver induced by 2,20-azobis (2-amidinopropane) (AAPH) and terc-butyl hydroperoxide (terc-BOOH); DPPH Radical sequestration (1,1-diffhenyl-2-picril-hydrazil) by the discoloration method. Hydrogel was successfully prepared by introducing portions of FA into the

cellulose skeleton. Ferulate hydrogel was a stronger antioxidant in the protection of tert-BOOH membranes than in aph-induced lipid peroxidation, with preservation of antioxidant activity for up to 2 h. For DPPH analysis it was found that ferulate hydrogel is eliminated very efficiently from this radical. The authors conclude the study by suggesting that this antioxidant biopolymer could be used in cosmetic and pharmaceutical fields and substantially shipped free radical damage and oxygen depletion.

To increase the rate of release of FA Ouimet et.al. [29] added ethylene glycol groups as the binding molecule between two FA molecules. The authors discuss profiles of synthesis, characterization and release of the drug of glycol-modified polymers, in addition to polymer cytotoxicity. In vitro release was performed by polymer discotheques to minimize interference from external effects (e.g., formulation additives). In this work, glycol groups were incorporated into the polymer skeleton to increase the rate of AF release. This addition of ethylene glycol promoted greater antioxidant activity and influenced the ability to strategically release ferulic acid at rates and concentrations relevant to topical applications, such as skin care products.

Peres et.al. [30] examined the combination of ethyl-hexyl triazone and bis-ethyl-hexyloxyphenol methoxyphenyl triazine with ferulic acid in order to obtain multifunctional sunscreens with antioxidant efficacy. Both UV filters are photostabilized molecules with low skin permeation and high efficacy at low concentrations, ideal characteristics for photoprotectors. The researchers evaluated the clinical safety of bioactive sunscreens and the effect of FA on improving the photoprotective and antioxidant efficacy of samples through Human Repeat Insult Patch Test (HRIPT) and phototoxic potential/photosensitivity, *ex vivo* antioxidant activity assay (performed based on tape striping technique) and SPF (estimated sun factor protection) *in vitro* and UVA PF (protection factor) *in vitro.* Oil-in-water emulsions that associate or not AF and UV filters were developed based on an anionic self-emulsifying agent. The samples presented good skin biocompatibility and no phototoxicity and photosensitivity. A synergistic effect was evidenced between FA and UV filters, as well as FA increased in vivo SPF by 37% and UVA protection factor (UVA-PF) by 26%. *Ex vivo* antioxidant evaluation and data showed that there was no tendency to increase antioxidant activity in the skin after treatment with the formulation. In vivo data indicated that PA intensified the photoprotection of formulations. In this research, the synergy between FA and UV filters led to the development of multifunctional sunscreens with photoprotective and antioxidant activities.

2.3. Technological optimization of ferulic acid

Chen, Liu and Fahr [31] presented a research aimed at obtaining an adequate vesicular system for the cutaneous release of ferulic acid and in the investigation of the influence of different vesicular systems on percutaneous absorption of FA. Different vesicular systems (conventional liposomes, Tween 80-based deformable liposomes, invasomes and ethosomes) containing ferulic acid were characterized for particle size distribution, zeta potential, vesicular shape and surface morphology, *in vitro* permeation of human skin and skin deposition. The experiments of permeation and skin deposition demonstrated that the permeation profile of ferulic acid through the membrane dand human stratum corneum and the deposition of drugs in the skin improved markedly using these vesicular liposomal systems. The effect of permeation and skin deposition was highlighted by the ethosomal system containing 18.0 mg/ml of ferulic acid with a skin flow (75 times greater than FA) and drug deposition on the skin (7.3 times greater than ferulic acid) significantly better. In this study, different liposomal systems containing FA showed different abilities to administer the drug to the skin or skin. Among these, ethosomes delivered a significantly higher amount of FA through the skin and also led to better epidermal deposition of the drug that would be high enough for antioxidant effects.

Harwansh et. al. [32] developed a nanoemulsion-based gel loaded with ferulic acid in order to ensure greater permeability and maximum antioxidant activity against UVA-induced oxidative stress in rats. The optimized FA-NE3 nanoemulsion was prepared by the spontaneous nanoemulsification method with an adequate proportion (20:30:50% p /p) of oil (isoestearyl isoestearate), aqueous system and Smix [surfactant (labrasol) and co-surfactant (plurol isostearique)], respectively, and incorporated into carpobo gel 940. The hairless abdominal skin of the rats was mounted in franz's diffusion cell with the side of the stratum corneum facing the donor compartment and the dermal side to the recipient compartment. The nanoemulsions were uniformly spread on the skin in the donor compartment and the samples were taken at predetermined time intervals for 24 h. The efficacy study of gel formulations loaded with FA as a photoprotective agent against UVA exposure was performed on the dorsal skin of rats for 8 days. In addition, antioxidant biochemical marker enzymes were estimated in the cutaneous tissue. The optimized gel formulation showed greater permeability to FA and higher UV protection activity. It raised the level of antioxidant markers and stopped the unwanted effects generated by ultraviolet radiation. This phenomenon attributed to encapsulated FA is linked to the higher potential for skin penetration when compared to its conventional gel.

The authors suggest that the formulation of nano-gel FA could be explored as a promising carrier for the distribution of actives to the skin.

Bairagi et.al. [33] investigated the potential of hydrogel based on polymeric nanoparticles loaded with ferulic acid in the healing of diabetic wounds *in vivo.* Ferulic acid-poly (lactic-co-glycolic acid) (FA-PLGA) nanoparticles were prepared by the nanoprecipitation technique and optimized using the central composite design. These nanoparticles were characterized for size, encapsulation efficiency and morphology. Finally, the effect of FA (oral and topical) on the healing of diabetic wounds was studied in diabetic rats induced by streptozotocin using the excision wound rat model. The dispersion of polymeric nanoparticles loaded with FA (oral administration) and hydrogel based on polymeric nanoparticles loaded with FA and carbopol 980 (topical administration) was used. *In vivo* studies have shown that topical and oral treatment of FA nanoparticles is effective in promoting wound healing in diabetic rats, where they epithet more quickly compared to the diabetic wound control group. In addition, the hydroxyproline content has increased significantly, the measurement of hydroxyproline is an index of collagen renewal and indicates that the healing process is taking place. According to the authors, the results indicate that FA significantly promotes wound healing in diabetic rats.

Aitipamula and Das [34] developed FA cocrystals for the composition of new topical formulations. The FA cocrystals were prepared using three cocrystalline sums relevant for skin care, such as urea, nicotinamide (NA) and isonicotinamide (INA), then incorporated into oleogel formulations. The cocrystals were widely characterized by thermal diffraction and X-ray techniques. In addition, in vitro release studies were conducted using franz diffusion cell and HT Tuffryn membrane® Polysulfone to evaluate the active release profile. Solubility studies have shown that cocrystal ferulic-isonicotinamide acid (FA•INA) shows higher solubility than the other two cocrystals and FA. Furthermore, the stability analysis of the formulations revealed that FA was more stable in formulations containing FA•INA or FA•urea cocrystals. The in vitro release studies showed sustained release of FA from the formulation that contained the cocrystal FA•INA, in this case, having FA in the cocrystal form led to sustained release/permeation. This will lead to prolonged action of the cocrystal-containing formulation after application on the skin. The authors suggest that the observed slow permeation of the cocrystal-based formulation may be due to the slower dissociation of the cocrystal into oleogel to release FA before permeation through the membrane.

366 Table 1 presents the summary of the articles discussed throughout this section
367 with information on authors, year of publication, country, application and analyzed
368 activity.

Table 1. Scientific articles on ferulic acid and evaluated activity

Ref.	Tittle	F.A and other actives	Main Activity	Tests	Year	Country
[19]	Ferulic Acid Stabilizes a Solution of Vitamins C and E and Doubles its Photoprotection of Skin	Association with antioxidant vitamin – Vitamins C and E	Improve stability and photoprotection	Chemical stability of the formulation based in the calculation of the antioxidant protection factor and other aspects. The formation of thymine dimers and the generation of keratinocyte apoptosis.	2005	US
[20]	Ubiquinone, Idebenone, and Kinetin Provide Ineffective Photoprotection to Skin when Compared to aTopical Antioxidant Combination of Vitamins C and E with Ferulic Acid	Association with antioxidant vitamin – Vitamins C and E	Photoprotection	*In vivo* Colorimetric mesurement methods of the induced skin er ythema and analysis of thymine dimers presence.	2011	US
[21]	A topical antioxidant solution containing vitamins C and E stabilized by ferulic acid provides protection for human skin against damage caused by ultraviolet irradiation.	Association with antioxidant vitamin – Vitamins C and E	Stabilization, photoprotection and antioxidant	Patch tests with measurement of erythema and sunburn cells and immunohistochemistry for thymine dimers and p53	2008	USA
[22]	Differential Effects of Topical Vitamin E and CE Ferulic Treatments on Ultraviolet Light B Induced Cutaneous Tumor Development in Skh-1 Mice	Association with antioxidant vitamin – Vitamins C and E	Photoprotection and antitumoral activity	*In vivo* Glutathione Peroxidase and Catalase Activity Assay eval uating the development of malignant skin tumors in mice.	2013	US
[23]	Protective Effects of a Topical Antioxidant Complex Containing Vitamins C and E and Ferulic Acid Against Ultraviolet Irradiation-InducedPhotodamage in Chinese Women	Association with antioxidant vitamin – Vitamins C and E	Antioxidant and photoprotection	*In vivo* evaluation of photolesion, skin erythema and biopsy of a skin area induced by ssUVR.	2013	China
[24]	Laser Assisted Delivery of Vitamin C, Vitamin E and Ferulic Acid Formula Serum Decreases Fractional Laser Postoperative Recovery by Increased Beta Fibroblast Growth Factor Expression	Association Laser and antioxidant vitamin - Vitamins C and E	Wound Healing	*In vivo* test of the effects and efficacy of a serum, using photographs, patient questionnaires, and molecular evaluation to analyse important aspects in the healing process.	2016	US
[25]	Effect of atopical antioxidant serum containing vitamin C, vitamin E, and ferulic acid af ter Q-switched 1064 nm Nd:YAG laser for treatment of environment-induced skin pigmentation	Association Laser and antioxidant vitamin - Vitamins C and E	Against hyperpigmentation	Single blinded, randomized trial occured and the were effects tes ted with digital photography, melanin and erythema index, mela sma severity score and global improvement.	2013	US
[26]	Protective effects of a topical antioxidant mixture containing vitamin C, ferulic acid, and phloretin against ultraviolet-induced photodamage in human skin	Association with antioxidant vitamin – Vitamin C and phloretin	Antioxidant and photoprotection	Erythema, presence of sunburn cells, thymine dimer formation, matrix metalloproteinase-9 and p53 protein expression.	2008	US
[27]	A novel dextran hydrogel linking trans-ferulic acid for the stabilization and transdermal delivery of vitamin E	Association with hydrogel and Vitamin E	Antioxidant and photoprotection	Inhibit lipid peroxidation in the microsomal membranes of rats induced *in vitro* by free radicals and the characterization of the release behavior and deposition in rabbit skin.	2008	Italy

[28]	Synthesis and antioxidant activity evaluation of a novel cellulose hydrogel containing trans-ferulic acid	Association with other substances - cellulose hydrogel with trans-FA	Antioxidant	*In vitro* test of inhibition of lipid peroxidation assay and DPPH Radical sequestration.	2008	Italy
[29]	Ferulic acid-based polymers with glycol functionality as a versatile platform for topical applications	Association with other substances - ethylene glycol groups	Antioxidant	*In vitro* release of Ferulic Acid, antioxidant activit using (DPPH) radical scavenging assayand, *in vitro* cytocompatibility studies using mouse fibroblasts cells.	2015	US
[30]	Ferulic acid photoprotective properties in association with UV filters: multifunctional sunscreen with improved SPF and UVA-PF	Association with other substances - ethyl-hexyl triazone and bis-ethyl hexyloxyphenol methoxyphenyl triazine	Antioxidant and Increase photoprotection	Human Repeat Insult Patch Test (HRIPT) and phototoxic potential/photosensitivity, *ex vivo* antioxidant activity assay and SPF (estimated sun factor protection) *in vitro* and UVA PF (protection factor).	2018	Brazil
[31]	Skin delivery of ferulic acid from different vesicular systems	Ferulic acid and vesicular systems	Antioxidant and skin permeation	*In vitro* permeation in human skin and drug deposition on the skin.	2010	Germany
[32]	Enhanced permeability of ferulic acid loaded nanoemulsion based gel through skin against UVA mediated oxidative stress	Ferulic Acid and nanoemulsion	Skin permeation, photoprotection and atioxidant	*Ex vivo* skin permeation study in the Franz diffusion cell and Efficacy study of the FA nanoemultion as an photoprotective agent.	2015	India
[33]	Preparation, Characterization and in-vivo evaluation of Nano formulations of Ferulic acid in diabetic wound healing	Ferulic acid and nanoparticles in gel formulations	Antioxidant, wound healing	*In vitro* drug release and in vivo test of wound area and % wound closure assessment	2018	India
[34]	Cocrystal Formulations: A Case Study of Topical Formulations Consisting of Ferulic Acid Cocrystals	Ferulic Acid in formulations containing urea, nicotinamide and isonicotinamide	Stability, solubility and behavior in the cocrystal formulation	*In vitro* Release (Membrane Permeation) Test, solubiity test, thermal characterization and powder X-ray Diffraction (PXRD).	2020	Singapore

3. Patent research and evaluation

This review was developed using as a guide the main patent database with the objective of understanding the evolution and tendency in the use of ferulic acid in topical formulations, between 2008-2019 The databases used for the research were the World Intellectual Property Organization (WIPO), European Patent Office (EPO), Instituto Nacional de Propriedade Industrial (INPI) e United States Patent and Trademark Office (USPTO).

The patent research was conducted between November 2019 and March 2020, utilizing the main words 'ácido ferúlico' in Portuguese and 'ferulic acid' in English. Right after the wider search the patents were counted and separated initially by year of publication. From this scenario, they were filtered using the IPC classification code A61K which includes medical preparations, dentistry, and hygiene. After the first phase, the patents that included topical applications were selected and organized by country of publication. Based on this strategy 510 publications were found, 253 of them on EPO, 245 on WIPO, 10 on USPTO and 3 on INPI as shown in Figure 3.

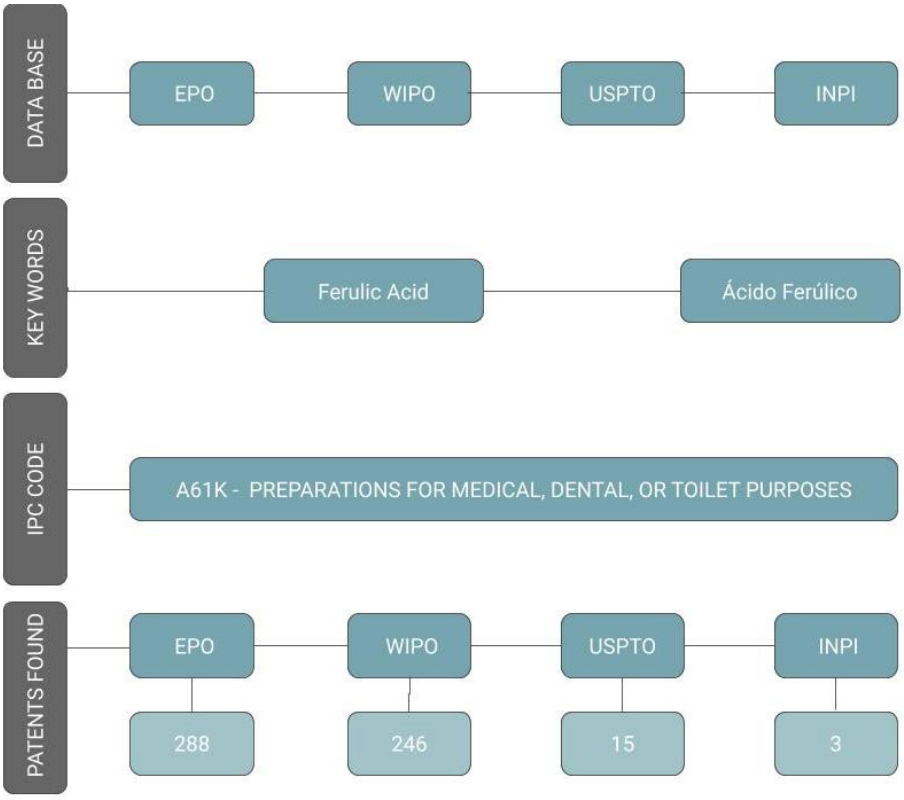


Figure 3 - Overal steps of the patents research and selection

The strategy was finalized by removing the double-ups resulting in a total of 290 patents, only the ones that presented the Ferulic Acid as one of the main actives in the

formulation were selected. After the removal of the double-ups the remaining patents were analyzed by the year of publication (Figure 4) showing a significant increase in the number of works published, the tendency can be observed especially looking to the number of publications in 2008 that were 4 and in 2018 that were the year of most publications with 38 patents publicated, similar to 2019.

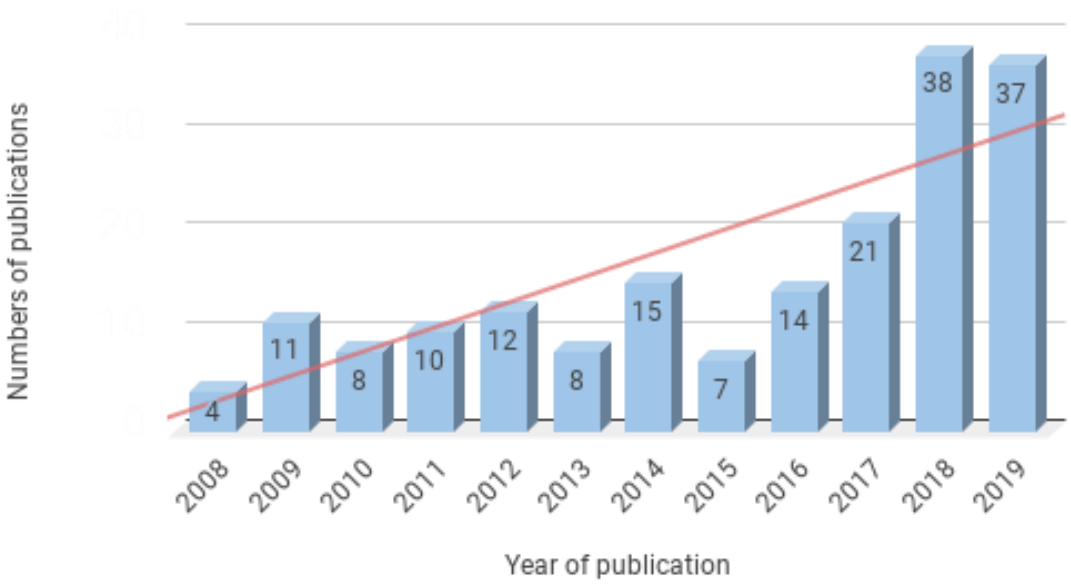


Figure 4 - Patents publication per year between 2008 and 2019 after application of inclusion and exclusion criteria

Related to the countries that the patents were published it was observed a significant difference between the Asian countries (especially China) and the occidental countries following the tendency of using the Ferulic Acid on topical formulations. China has a larger percentage of publications with 69% of the patents, followed by the United States 10,9 %, Japan 6,1%, Korea 5,8% and Brazil as well as the Patent research and evaluation as shown in Figure 5

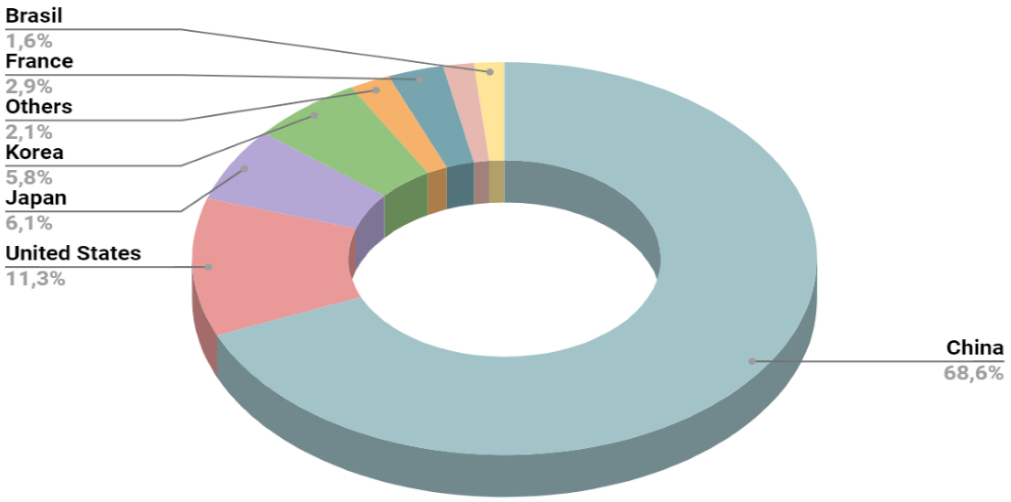


Figure 5 – Patents publications on the use of ferulic acid in topical formulations per country

4. Ferulic Acid in topical formulations

It is known that the ferulic acid occurs naturally in plants, mainly in rice and maize bran. It has a strong antioxidant activity, a potential of application in various pharmaceutical formulations, and pharmaceutical porpuses. The versatility of this compound allows it to be present in formulations acting isolated or combined with other actives, having a synergic effect and giving a better result [8,35, 36].

This substance presents low water solubility, being soluble in ethanol and other organic solvents, low stability when exposed to light ant temperature higher than 80ºC. Characteristic that associated with its low toxicity and wide range of application in topic formulations, opened the space for patents and publications in this area of research that has the Ferulic Acid in preparations with the most diverse technologies with the goal to facilitate the incorporation in formulations and improve the stability [37, 38, 39].

4.1. Therapeutic activity in formulations

4.1.1 Antioxidant

Antioxidant substances protect cells from the damage of oxidative stress by scavenging free radicals, inhibiting superoxide and acting against the longterm effects of the reactive oxygen species (ROS). The topical application of antioxidants is broadly used in skincare as actives to promote skin health, prevent aging and skin cancer [40].

The patent US20140107046 presents the combination of at least one flavonoid (baicalin and taxifolin) and ferulic acid effect in an aqueous formulation. The flavonoids ratio is about 0.01% to about 20% based on the total weight of the composition. It's been reported that the combination of polyphenols and other antioxidants shows strong synergic effects in comparison to the individual compounds, increasing the antioxidant activity. One hydrotrope (caffeine or nicotinamide) or one diol was added to the increase in the solubility of the antioxidant in water.

The antioxidant effect in this composition was analyzed comparing the oxygen radical absorption capacity assay (ORAC) of the single compound and the combinations, the synergistic effect is present when the ORAC result of the combination is more than 25% higher than the expected based in the value of the substance alone. The Ferulic Acid isolated showed an ORAC of almost 15000 μmolTE/g, while the vitamin C had less them 5000 μmolTE/g, the ferulic acid had an antioxidant property almost 3 times higher than the vitamin C, but when combined, the synergic effect shows an even stronger capacity.

In the first formulation which is a water-based solution, the synergic effect was observed when the baicalin and the Ferulic acid were combined with another antioxidant such as vitamin C or resveratrol when the baicalin or resveratrol was removed from the formulation the antioxidant effect from the formulation the effect wasn't as strong. This shows that the Ferulic Acid has a great activity as an antioxidant, but combined with other actives, the benefit to the skin is considerably increased.

Still using the ascorbic acid, which is a well-known antioxidant compound, the patent KR20180073305 used the antioxidant activity of vitamin C as a comparative with the ferulic acid. The Ferulic acid scavenging activity was confirmed with the FSC50 method that measures the necessary amount of the substance needed to reduce 50% of the free radicals of DPPH, confirmed by ELISA reader, which for the F.A. showed 4.5 ppm compared with 7.0 ppm for the Ascorbic Acid, attributing the ferulic acid an excellent antioxidant effect.

4.1.2 Anti-aging

It is well known that the natural production of collagen (responsible for the firmness and lift of the skin) and hyaluronic acid (the main substance of water retention and skin hydration) decreases with aging due to internal and external factors like stress, pollution, and exposure to radiation [36]. With that in mind and focusing on improving skin wrinkles, the invention KR20110101727 shows a composition of Peonyflorin,

Cardamonine and Ferulic Acid that acts inhibiting the collagenase activity, improving ferulic acid production and stimulating the collagen synthesis [41].

In the first test, the inhibition of the collagenase was tested using a sample with 1% of retinoic acid as the positive control, another with the actives and the negative control had only the base substracts with no other component. As it was a colorimetric reaction, the color absorbance was measured using a fluorometer. The results for the positive control was an inhibition rate of 40% and the three samples that had the ratios of peonyflorin, cardamonine and F.A. respectively between 1-3: 1-3: 8-4 presented an inhibition rate of 62 to 68%.

The collagen synthesis was confirmed with an in vitro test using a culture of fibroblasts and the same 3 ratios of the compounds showed and excellent synergetic action with a synthesis promoting effect 26% higher than the positive control that was 52.8 μg/ml of vitamin C. Evaluating the hyaluronic acid expression (done in a culture of mouse fibroblasts), comparing the results of the three substances isolated and combined in concentrations of 1 and 10 μg/ml, it was observed that the synergic effect was the most effective, but comparing the isolated compounds, Ferulic Acid was the one that had the best result.

Because of the studies that not only associate the Ferulic Acid with its antioxidant property but with the collagen production stimulation, the invention BR102017016356-3 proposed a composition of Ferulic Acid and Hyaluronic Acid associated with radiofrequency therapy that's widely used in treatments improving the elasticity of the skin and increasing in this composition, the antiaging effect.

4.1.3 Antiinflammatory

The patent KR20110068258 showed the synergetic effect of Ferulic Acid in compositions with at least one of the following components Polydatin and 2-methoxycinnamaldehyde, variating the weight ratio from 1:0.1 to 1:20 between two components of the three cited before. The effect of 21 different compositions with various ratios was compared initially measuring the production amount of Prostaglandine 2 (PGE2), and the relative inhibition rate of the enzyme Phosphodiesterase 2 (PDE2) in cell culture, compared with alpha-bisabolol, which was used as the positive control. The same method was used in experiment 2, but only with the two compositions that had the best previous results, Composition 12 (that had 0.5%

of Polydatin and 1.5% of 2-methoxycinnamaldehyde) and Composition 19 (with 0.5% of Ferulic Acid and 1.5% of 2-methoxycinnamaldehyde) comparing their effects in four different concentrations from 0,0001% up to 0.1%. Showing that the combination of the anti-inflammatory component added with ferulic acid had an excellent synergic effect of inhibiting the production of very potent PGE 2 without being toxic at 0.1% concentration.

At last a third experiment was done with an in vivo method applying 2 mg of arachidonic acid in the right ear of each mouse once a day for four days, leaving de left one as the control. The anti-inflammatory effect was determined based on the group that was treated with the arachidonic acid, in comparison to the formulated topic treatments using the measurement of the edema and added to an equation that calculated the inhibition rate of the compositions. Showing that the combination of the 2-methoxycinnamaldehyde with the ferulic acid had an antiinflammatory effect 3 times higher them if it was used isolated, along with the antioxidant potential, this association can lead to great results and a wide variety of therapeutic applications.

4.1.4 Prevent adipose overload

Adipose overload has become more common because of unhealthy habits especially in developed countries, with a high intake of processed foods and not enough practice of physical activities. A consequence of this lifestyle is the build-up of excess fat in the hypodermis that is intimately linked with a systemic inflammatory reaction on the body, a decrease in insulin sensibility leading do chronical and serious diseases. This topic has become more than an aesthetic subject, more importantly, a health issue.

Studying the Ferulic Acid lipolytic effect, the patent FR2907338 presented in their first in vitro test that 0,2% of Ferulic Acid added to a culture of human adipocytes increased in 24% the release of glycerol into the culture, which shows a significant lipolytic action. Another test demonstrated the competing effect of the Ferulic acid in the insulin receptors of adipocytes, competing at a level of - 34% with the insulin. Acting like a mediator that inhibits lipogenesis after binding with the receptors instead of the insulin. In that way, the Ferulic Acid inhibits the insulin activity in lipogenesis that now reduced the synthesis and secretion of the lipoprotein lipase.

4.1.5 Whitening

Tyrosinase inhibition leads to a decrease in melanin production, increasing the brightness and inhibiting hyperpigmentation on the skin, especially when the skin is exposed to the sun. Invention CN105581919 presented a ferulic acid phospholipid complex that aimed to have a great whitening effect, especially by increasing the bioavailability of the F.A by improving its physicochemical properties. The patent showed great results in the inhibition rate of the tyrosinase and the inhibition in cell melanin synthesis, done by *in vitro* experimental methods. Added to the previous tests, the experiment run with 30 volunteers between 25-45 years showed an increase in skin brightening and reduced facial melanin spots on the skin. It even suggested three formulations being a cream, an emulsion, and a skincare oil.

Another method that had a skin whitening effect was in the publication US2013345307 that brought a system of skin rejuvenation including first a chemical pell and than a booster that should be applied after the exfoliation and removal of dead skin cells, what makes the booster have a better effect penetrating more effectively on the skin. When comparing the effect of ferulic acid, and other phenolic compounds isolated and in combinations, the one that had the F.A associated with the phloretin, vitamin C and E had the best result. Especially because both the F.A. and the phloretin have whitening effect with different mechanisms, both modulating the melanocyte and fibroblast. The disclosure products indicated had about 2% to 15% of ferulic acid in their formulations, the effect of the treatment could be seen in volunteers that had treated their face, hand, and V neck region showing great results in alleviating sun and acne spots as well as smoother skin texture.

The invention CN103637924 also showed a composition that focused on the synergic effect containing ginsenoside Rb1 and Ferulic Acid as the main actives in a face mask, the indicated ratio by weight was 18 parts of ginsenoside Rb1 and 15 parts of ferulic acid. Finally, the patent BR102015003242-0 A2 showed the whitening effect to treat melasma with a formulation that has no serious side effects as the traditional treatments, combining at least other two antioxidants with the F.A. The M.A.S.I. (Melasma Area and Severity Index) evaluation in 11 volunteers showed an average improvement in the aspect of the skin by 25.3% after 28 days of treatment.

4.2. Improving the Ferulic Acid characterists

Ferulic Acid has a wide range of activities, from antioxidant and antiinflammatory to preventing fat accumulation and inhibiting melanin, but its application in formulations is limited due to its low water solubility and molecule instability, leading into physicochemical limitations.

One of the main study areas that cover the FA is the application of technologies and new methods to improve the interaction and stability of the compound molecule in formulations, with that in mind the invention CN101485447 explored the inclusion of F.A. in cyclodextrins, creating a compound that can be applied not only in pharmaceutical and cosmetic industry, but in the veterinary and food industry too. Similar to the patent BR 102016022392-0 that proposed a multi-component system, complexing the molecule into cyclodextrin and hydrophilic polymers which provides a synergic effect increasing the molecule solubility, stability and the antioxidant activity when compared to the FA alone.

Another invention CN105581919 proposes a Ferulic Acid phospholipid complex to improve the compound bioavailability in formulations. The solubility and Free radical scavenging experiments showed great results in both tests, the first one increased the solubility of the F.A in water and the second one has a better scavenging effect than the Ferulic Acid alone. They also tested the permeability and the transdermal permeation of the combined FA with time. The accomplished results showed that the Ferulic Acid phospholipid complex has good permeation performance, better solubility and improved penetration in the skin.

620

Table 2. Main patents and highlited information.

Ref.	Code	Tittle of the patents	Activity	Tests performed and cited in the patents	Year	Country
[41]	US20140107046	Cosmetic compositions containing at least one flavonoid and Ferulic Acid	Antioxidant	Oxygen radical absorption capacity assay (ORAC)	2014	US
[42]	KR20180073305	Cosmetic composition for preventing skin aging by heating	Antioxidant and Antiaging	Scavenging activity FSC50, Production of MMP-1 (Matrix Metalloproteinase-1) and MMP-3 for Ferulic Acid Treatment in Heat Treatment Conditions and Production	2018	Korea
[43]	KR20110101727	Composition for improving skin wrinkle	Antiaging	Inhibitory effect of collagenase activity, Confirmation of collagen synthesis promoting effect (quantified using a PICP EIA kit) and Evaluation of Increased HAS2 Expression in Mouse Fibroblast NIH3T3. Confirmation of skin wrinkle improvement through panel test.	2011	Korea
[46]	KR20110068258	Composition for anti-inflammatory	Antiinflammatory	Production of Prostaglandin 2 (PGE2), Relative inhibition rate of the enzyme Phosphodiesterase 2 (PDE2) in cell culture	2011	Korea
[47]	FR2907338	Use of ferulic acid, its salts and/or derivatives as lipolytic agent to prepare a cosmetic and/or pharmaceutical composition to prevent and/or treat the adipose overloads and/or cellulitis, by systemic and/or local administration	Lipolytic	Enzymatic determination of glycerol in culture cells and Competition of the substance for insulin receptors in a co-culture system of keratinocytes and adipocytes	2008	France
[51]	BR102015003242-0 A2	Composição cosmética e uso da mesma	Whitening	The composition was tested in volunteers the M.A.S.I. (Melasma Area and Severity Index)	2016	Brazil
[49]	US2013345307	Systems and methods for skin rejuvenation	Antiaging and Whitening	The product was applied in the face, hand and neckline of the volunteers and compared the before and after	2013	US
[48]	CN105581919	Ferulic acid and phospholipid complex and application thereof to preparation of skin-whitening cosmetics	Whitening	In vitro tyrosinase inhibition test of ferulic acid phospholipid complex and Inhibition test of cell melanin	2016	China

5. Conclusion

Ferulic Acid is widely used in the food industry, veterinary, pharmaceutical, and cosmetic fields [11]. It is a well-known compound that has been showing great responses in antiinflammatory, lipolytic, brightening, anti-wrinkle, and antioxidant activities as confirmed in the patent tests highlighted in table 2 of this review [12] [16] [54]. Wich opens doors to explore even more it's properties, especially in the field of topical formulations, extending to the dermo-cosmetic area. Chronical dermatological disorders like dermatitis, rosacea, psoríase, and acne could be a study target to Ferulic acid activity especially since these diseases have been increasing in the population [13].

In the literature prospection, it was found that studies with AF for cutaneous application began in the 2000s and initially the research was concentrated for its use associated with other antioxidant substances, especially vitamins C and E. There are few studies that explore the molecule alone, but when it occurs it is always in an attempt to perform a technological improvement to ensure stability and good skin delivery. In general, the articles always describe some assay of i*n vitro* or *in vivo* character for evaluation of antioxidant and/or photoprotective activities.

Through the selection of the patents it was observed that although China is the country with a higher percentage of patents published, most of them are methods and compositions of products using the ferulic acid. Overall only a few of the inventions published had tests *in vitro* and/or *in vivo* and these were the ones that were most explored in this review. But the topic that has been growing more lately and has the largest applicability is the development of new technologies and methods to improve the physicochemical properties of the Ferulic Acid, delivering a more stable active that has more efficacy, especially against Reactive Oxygen Species [55,56].

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