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Recent Updates on the Power of Caffeine Nano Formulations to Treat Dermatological Problems: A Natural and Sustainable Drug and Cosmetic Preparation

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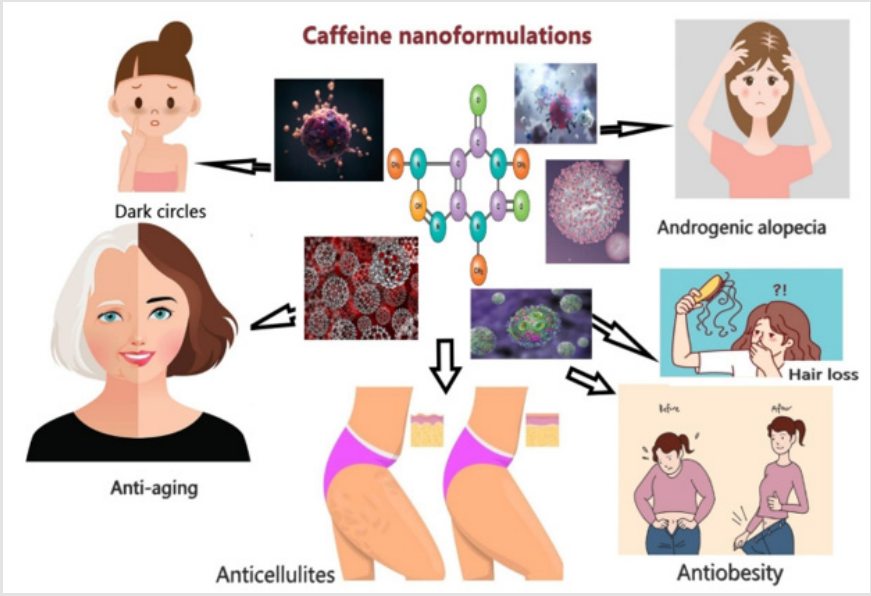
ABSTRACT

About 80% of people around the world consume caffeinated drinks daily. Drinking coffee can't be considered harmful to the skin, but it does not offer all the benefits of using caffeine topically. Mostly caffeine has been known for its oral uptake since a few years ago, when it's physicochemical and permeation properties were discovered. The high biological activity of caffeine and its ability to penetrate and diffuse through the skin barrier gave rise to a significant increase in its use in cosmetic preparations. According to Advanced Dermatology, American women spend about $722 yearly on cosmetics, skin care, and hair products. In the UK, women spend 450 euros yearly on cosmetics. In the Middle East, Saudi women are the greatest spenders on cosmetics, then Emirati women ($909 and $694), respectively. Women prefer natural cosmetics all over the world. This review was conducted to illustrate the diverse topical uses of caffeine and its different nano formulations. This was done by searching through articles published over the last 10 years using different search engines. Caffeine and its nano formulations, such as nanoemulsions, microemulsions, silver and gold nano particles, solid lipid nanoparticles, copper oxide nanoparticles, liposomes, nanohydrogels, nanocrystals, nano capsules, and nanotubes, are used in many pharmaceutical products for treating dark circles, anti-cellulite, anti-obesity, and the problem of hair loss. Using caffeine for dermatological purposes is considered a step toward a natural and sustainable way of treating different skin disorders instead of the common use of chemical drugs possessing several side effects (Graphical Abstract).

Keywords: Androgenic Alopecia; Cellulites; Skin Cancer; Obesity; Anti-Aging; Dosage Forms

Abbreviations: CNS: Central Nervous System; NSAIDS: Non-Steroidal Anti-Inflammatory Drugs; DHT: Dihydrotestosterone; PDE: Phosphodiesterase Enzyme; CAMP: Cyclic Adenosine Monophosphate; PDI: Polydispersity Index; HOCM: Hair Organ-Culture Model; GIT: Gastrointestinal Tract; UV: Ultraviolet; w/v: Weight by Volume; mTORC1: Mammalian Target of Rapamycin Complex 1; PPAR: Peroxisome Proliferator-Activated Receptor; WHO: World Health Organization; AMA: American Medical Association; FDA: Food and Drug Administration; SLN: Solid Lipid Nanoparticles



Graphical Abstract.

Introduction

Cosmetics is among the largest economic industries worldwide [1]. Being the fastest-growing market, in 2021 the market share of cosmetics increased to reach 500 billion dollars [2]. The obsession of women to obtain perfect baby skin never stops. Unfortunately, after the age of 30, the natural skin aging process begins to proceed, which is considered one of women's biggest fears [3]. Among the marked effects of social media is the increase in women's awareness of the excessive use of chemical products that may harm their skin [1]. Pharmaceutical companies are greatly contributing to the world's economy to the extent of making 1.27 trillion US dollars in profits yearly; unfortunately, they are a major cause of increasing carbon footprint to 1.9 Mt CO2 [4]. All of the world nowadays is shifting towards the use of natural products in the pharmaceutical industry, which have been proven to be potent, sustainable, and cost-effective. Sustainability means to meet this generation's demands without affecting the upcoming generations negatively [5]. The sustainability in cosmetics preparation, manufacturing, and use has been developed [6]. Sustainability in cosmetics begins with the choice of raw materials by using green chemistry, recycling of different food products, and reuse of water.

Caffeine is considered the most widely consumed central nervous system (CNS) stimulant worldwide [7]. It is a plant alkaloid, and its chemical name is 1, 3, 7-trimethylxanthine. It is present naturally in tealeaves, cola, nuts, cocoa, and coffee beans. Caffeine is commonly ingested in tea, coffee, chocolates, and many energy drinks [8]. Also, it is an important component in many medications for the treatment of pain if it is used in combination with analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs), e.g., ibuprofen, as well as paracetamol [9], and for the treatment of migraine if it is combined with ergotamine [10]. Caffeine has been used as a fat burner and appetite suppressor for weight loss [11]. Moreover, it is used as a bronchodilator for the treatment of asthma [12]. Many studies have been conducted to provide evidence of the potency and efficacy of caffeine in the treatment of a wide range of diseases. Caffeine is widely used in dermatology for the treatment of many skin disorders and also in cosmetics preparations owing to its ideal absorption by the skin layers [13]. Caffeine, as a hydrophilic compound, gives rise to faster absorption by skin barriers, which has increased its use in topical preparations [14].

Among major pharmaceutical industry problems is poor water solubility of drugs [15]. About 60% of drug candidates and 40% of approved drugs since 1995 were considered water-insoluble [15,16]. Poor water solubility of drugs gives rise to poor dissolution, absorption, and subsequently low bioavailability and therapeutic efficacy [17]. Enhancement of solubility of poorly water-soluble drugs was done by different techniques [18]. Nanotechnology in drug delivery is considered one of those techniques that enhances the water solubility of poorly water-soluble drugs [19]. This is done by decreasing the particle size of the drug to reach a nanosize ranging from 10 to 100 nm [19]. So, nanoparticles are considered a more advantageous drug delivery system than the conventional ones [20]. Among those advantages are enhancing a drug's bioavailability, stability, shelf life, ease of encapsulation, ease of adsorption, providing controlled drug release, and targeted drug delivery [17]. The application of nanotechnology

emerged as a revolution in the dermatology and cosmetics world [21]. It enhances penetration of different drugs into deeper skin layers, giving rise to much better absorption and therapeutic efficacy [22]. By the aid of nanotechnology, different skin conditions were properly treated andalso prevented [22]. Among those conditions are acne, melanoma, hyperpigmentation, alopecia, fine lines, psoriasis, vitiligo, and others [22]. Besides treatment of skin conditions, nanotechnology offered very effective and elegant skin care products [23]. Sunscreens prepared by nanotechnology techniques offer highly powerful protection against UVA as well as UVB rays [23]. This review provides a detailed image of the most common uses of caffeine for the treatment of different skin disorders, such as dark circles, wrinkles, cellulite, hair loss, androgenic alopecia, skin cancer, sun protection, obesity, and others. It also gives a view on caffeine's major side effects, as well as the different caffeinated dosage forms present in the market including the recent ones. Different ways to increase caffeine solubility, bioavailability, and subsequently its efficacy as liposomes, nanoemulsions, metallic nanoparticles, nanocrystals, and solid lipid nanoparticles were also illustrated. This aims to provide a natural and sustainable way for many females and males to solve their skin problems properly.

Main Text

Effect of Caffeine on Androgenic Alopecia

Androgenic alopecia is among the most common hair loss problems that threaten both males and females [24]. In their middle ages, about 20 to 50% of males and 30% of females are affected by androgenic alopecia [25]. This is a hereditary case characterized by exaggerated loss of scalp hair, especially the terminal part [24]. Androgenic alopecia occurred as a result of binding of dihydrotestosterone (DHT) to androgenic receptors of hair follicles which resulted in thinning of hair and decreasing hair follicles [25]. The FDA had approved two different drugs for the treatment of androgenic alopecia with different mechanisms [25]. The first FDA-approved drug is "Finasteride" which acts by decreasing DHT synthesis [25]. The second drug is "Minoxidil" which is the most common drug used for the treatment of hair loss and to stimulate the regrowth of hair. It is applied topically to the scalp. It acts as a vasodilator, which allows more blood and nutrients to reach the hair follicle, stimulating its growth [26]. It also acts by opening potassium channels [25]. Despite being very effective in the treatment of hair loss, minoxidil gives rise to a serious side effect which is its liability to cause hair loss after stopping its use for several months [26]. Many patients stopped minoxidil treatment because of its irritant effect and also because it stimulates body hair growth [27]. For all of those reasons, the use of minoxidil for the treatment of hair loss as well as androgenic alopecia has been retarded, and searching for other natural sources has begun. Caffeine has a significant effect in the treatment of androgenic alopecia because of its ability to both oppose DHT effect counteracting hair thinning and also inhibiting phosphodiesterase (PDE) enzymes, which in turn increases concentrations of intracellular cyclic adenosine monophosphate (cAMP), which activates some enzymes, increasing lipolysis and cell energy and promoting hair growth [28].

Several studies were done to illustrate the pharmacological role of caffeine in the treatment of androgenic alopecia. In 2007, Fischer et al., conducted an in vitro study illustrating the effect of caffeine on androgenic alopecia [29]. Hair follicles from 14 men volunteers were in vitro cultivated for 120-192 h and were treated with different caffeine concentrations, the daily hair shaft elongation was measured [29]. Caffeine proved to possess the ability to counteract androgen dependent hair loss and it can stimulate hair growth with 0.001% and 0.005% concentrations [29]. Another study was done by Otberg, et al. [30] they prepared caffeine shampoo which proved very fast absorption through hair follicles within 20 min of its application [30]. In 2018, Bussoletti, et al. [31] evaluated the effect of caffeine shampoo in treatment of female's androgenic alopecia [31]. The effect of caffeine shampoo on androgenic alopecia in females was compared with controlled shampoo [31]. A hair pull test was done and both preparation was compared at 6 months, caffeine shampoo gave very promising effect regarding to numbers of hairs pulled through the 6 months [31]. In addition, caffeine shampoo decreased hair loss and increased hair strength [31]. A study was done to study the effect of caffeine in a hair organ-culture model (HOCM). At a caffeine dose of 1000 μg/ml, a 100-fold increase in hair follicle length in the HOCM appeared [28]. Also, a study was conducted, and it proved that the combination of both caffeine and minoxidil gives more promising results in the treatment of hair loss than using minoxidil alone [28], as shown in (Figure 1). Furthermore, Caffeine promotes hair follicle growth in 0.005%–0.0005% concentration as it stimulates hair shaft elongation in males as well as females, and this was reported by Visconti, et al. [13].

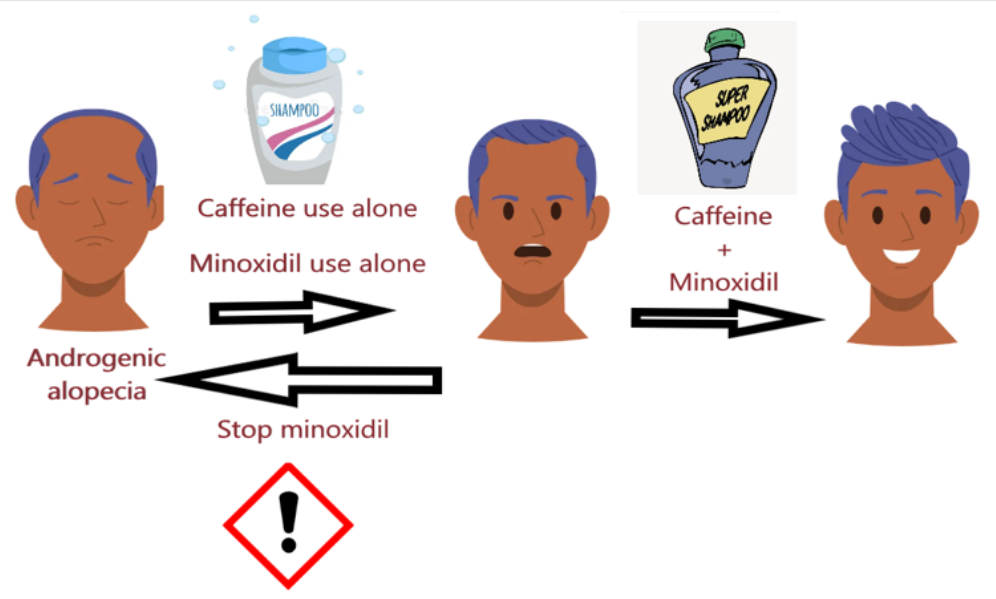


Figure 1: Effects of both caffeine alone, minoxidil alone, and combination of both caffeine and minoxidil on treatment of androgenic alopecia.

Effect of Caffeine on Dark Circles

Aging signs commonly begin to appear around the eyes; this place is fragile and delicate. The dermis (inner skin layer) becomes thinner because the division of the skin is slower, so collagen and elastin fibers loosen, leading to skin surface depression and a decrease in the elasticity of the skin [32]. As a result of being a powerful vasoconstrictor, caffeine can efficiently nourish the skin in this area [32]. Besides its ability to reduce wrinkles as a result of being a powerful antioxidant [32]. A combination of several vitamins as vitamin E and C are used with caffeine as antioxidants for the treatment of wrinkles and improving skin condition this product is available in the market from skin medica company [32]. Also, a study was conducted which investigate the effect of combining both caffeine and vitamin K for the treatment of wrinkles and dark circles around the eyes. Vitamin K role is to improve blood circulation around eyes, to strength blood capillaries at this area so it eliminates dark circles. The study succeeded in the preparation of pads enclosing both caffeine as well as vitamin K which appeared to be effective in the treatment of dark circles in a duration of only three weeks [32]. In 2011, a study was done to investigate the effect of using caffeine gel in reducing puffy eyes, which means edema and darkness around eyes [33]. The gel was prepared and in vitro skin permeation as well as in vivo evaluation of puffy eyes were done [33]. Caffeine gel has two mechanisms to decrease eye puffiness; the first one is vasoconstriction, and the second one is the cooling effect provided by the gel as shown in (Figure 2).

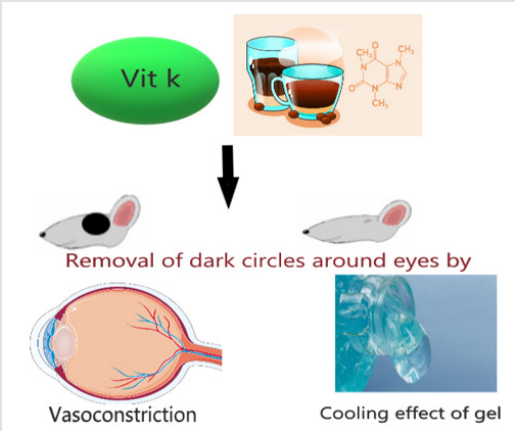


Figure 2: Effect of both vitamin K and caffeine on treatment of dark circles around the eyes.

Anti-Aging Effect of Caffeine

The major cause for skin aging and appearance of wrinkles is the oxidative stress [34]. Oxidative stress is originated from dissimilarity between reactive oxygen species and antioxidants; either leakage of antioxidants or increase in reactive oxygen species [34]. Oxidative stress is the main cause of many diseases affecting the whole human body, among those diseases are cancer, brain disorders, respiratory diseases, cardiovascular diseases, kidney diseases, gastrointestinal tract (GIT) problems, and others [35]. Many components of coffee are considered antioxidants for the treatment of oxidative stress and subsequently acting as anti-aging as caffeine chlorogenic acid, melanoidins and hydroxycinnamic acids [34]. Caffeine affects aging signs by decreasing the mammalian target of rapamycin complex 1 (mTORC1), this will extend the duration of life of fission yeast [36]. On comparing effects caused as a result of ingestion of regular (caffeinated) as well as decaffeinated coffee in aged mice, it revealed that the ingestion of caffeine has a significant increase in their food and water ingestion and their movement as well. Both types of coffee are able to decrease levels of free fatty acids in the plasma of those mice and increase ATP in their livers [36]. (Figure 3). Protein levels of peroxisome proliferator-activated receptor (PPAR) α which is crucial in lipid β-oxidation is increased as a result of mice ingestion of decaffeinated coffee also [37]. Phosphorylated-mTOR is decreased as a result of coffee ingestion which is important in aging process so antiaging effect is proved [36].

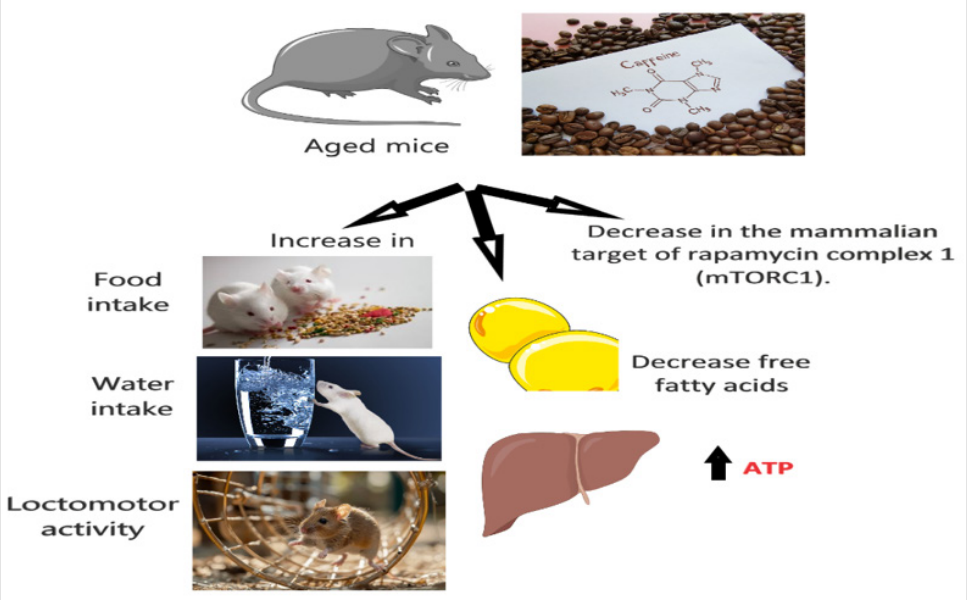


Figure 3: Physiological effects occurring in aged mice because of coffee intake.

Effect of Caffeine on Cellulite

Cellulite is a skin condition occurring in a wide range of females; the skin is characterized by strange appearance which looks like orange peels [38]. It occurs commonly as a result of deposition of fats in some places in the body as hips, thighs and buttocks [38]. Cellulite is more common in females than males this is due to differences in fat deposition in both male and females. The cellulite structure in females is vertical, while it is present with 45° in males. Women, particularly who are older than 20 years old exhibits more cellulite and it is considered very annoying for them as it is cosmetically non-appealing [39]. Many factors are associated with the appearance of cellulites including environmental, genetic, and hormonal [39]. An unhealthy lifestyle as an intake of fat-rich diet, fast food, and a decrease in physical activity is commonly accompanied by an increase in the incidence of cellulite [39]. Caffeine proved its efficacy in treatment of cellulites as mentioned in many studies as it has the ability to break-down fats as it is an inhibitor for PDE enzyme which increases level of cAMP in the cells [40]. Studies were done to investigate the effect of using caffeine on decreasing cellulite and its slimming ability. A study was done in 2015, it investigates the efficacy of using a topical slimming cream prepared using a mixture of caffeine in 3% and xanthenes on cellulites [37]. The slimming cream was applied two times per day for 6 successive weeks, the change in the severity of cellulites was determined using a scale. Finally, the study proved that this cream should efficacy as well as safety in the treatment of cellulites [37]. Hamishehkar, H. et al. [41] succedded in formulating hydrogel of caffeine-loaded solid lipid nanoparticles which proved its efficacy in treatment of cellulite [41], (Figure 4). The sustained release hydrogel which acts for 24 h, proved its efficacy both in in vitro as well as ex-*vivo* in rat's skin.

The reason for this efficacy was the small particle size of the solid lipid nanoparticles 94 nm and its high encapsulation efficiency 86% [41]. On comparing, the flux of caffeine in rat's skin in both solid lipid caffeine hydrogel and the ordinary caffeine hydrogel, the flux was 3.3 times greater which reflects that solid lipid nanoparticles are promising carriers for caffeine. Another study was conducted in 2018; it also proved the efficacy of caffeine topical preparation for treatment of cellulites. Puviani, et al. [37] mentioned that a topical cream consisting of caffeine, escine, beta-sitosterol, and sodium chloride in a concentration of 13%, was applied daily for a month on thighs [37]. Further study to confirm the efficacy of caffeine in the treatment of cellulites was done by Kassem, et al. [42]. Caffeine loaded nanostructured lipid carriers were prepared using both high-speed homogenization and ultrasonication. The experimental design used was 32 full factorial design to study the effect of both total lipid percentage and liquid lipid percentage on the formulation's particle size, zeta potential, polydispersity index (PDI), and finally viscosity of the preparation. The optimum formula possessed 318.8 nm, 0.253, −41.1 mV, and 18.0 Pa.s for particle size, PDI, zeta potential, and viscosity. The optimum formula succeeded in increasing caffeine flux into the rat's skin by 2 folds more than the plain caffeine gel and 1.4 times more than the marketed caffeine gel [42].

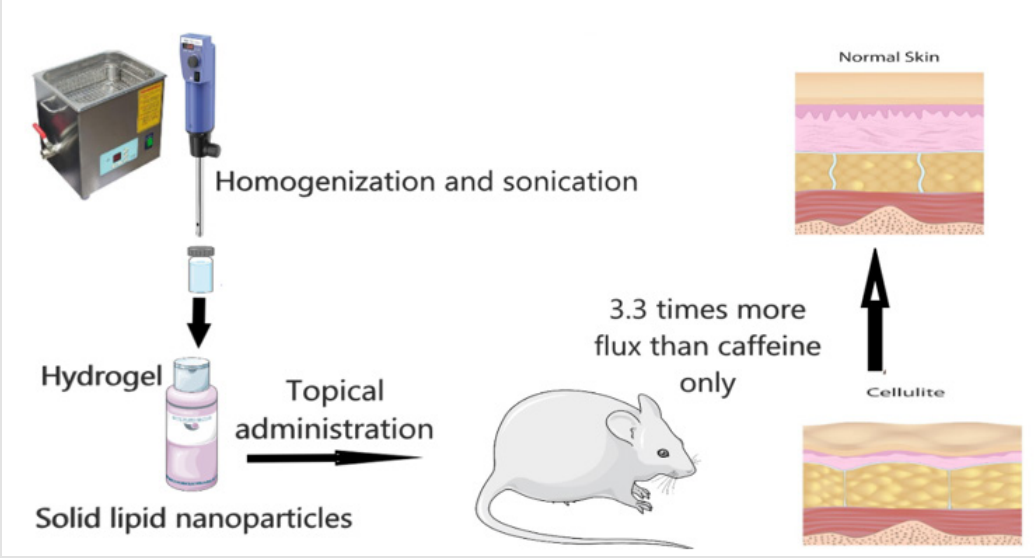


Figure 4: Effect of topical administration of caffeine solid nanoparticles formulated as hydrogel on cellulites of rats.

Effect of Caffeine on Skin Cancer

Melanocytes are the cells which gives the skin its distinctive color, the most frequent types of cancers are melanoma and non-melanoma skin cancers [43]. Cancer of melanocytes is known as melanoma which is a very dangerous type of cancer that may exist. It is considered a very common type of cancer occurring very frequently its cause may be direct contact with the UV (ultraviolet) sun rays or others [44]. On the other hand non- melanoma skin cancer is subclassified into basal cell carcinoma and squamous cell carcinoma of the skin, UV rays also may give rise to these types of skin cancers [45]. Caffeine was reported to be effective in the treatment of both skin cancer types as shown in (Figure 5), it can be administrated either by topical or oral route [46]. Among all metabolites of coffee, caffeine was the only one that proven to be effective against UV induced skin cancer as reported by Lu, et al. [47]. Three studies were conducted, and they proved the efficacy of topical caffeine in the treatment of skin cancer. The first study was done in 2005, it reported the efficacy of topical caffeine taken daily for 5 successive days in a dose of 6.2 µmol for the treatment of skin cancer in mice [47]. The second study was done in 2007, caffeine was dissolved in acetone in 1-2% w/v and it was administrated topically to mice suffering from squamous cell carcinoma [48]. The third study was done in 2016, it reported the efficacy of topical caffeine in a dose of 547.32 ± 1.68 µg mg−1 in treatment of UV-induced photoaging in mice [49].

Figure 5: Ability of caffeine in treatment of melanoma.

Effect of Caffeine in Skin Protection

UV rays are classified into three types according to their wave lengths UVA, UVB, and UVC [50]. UV rays with longer wavelengths are able to give higher penetration for skin layers, so UVA rays are able to penetrate skin layers deeply. UVB are known to penetrate the epidermis only and don't reach deeper skin layers, so they cause skin burn [50]. Caffeine has the ability to protect the skin against burns and damage because of its ability to protect the skin against UVB rays [46]. In 2019, a study was done to evaluate the sun protection ability of caffeine, a sunscreen was prepared and it was tested in vitro as well as in vivo on ten healthy volunteers [51]. The study proved the ability of caffeine to protect against UVB without causing any skin redness or inflammation [51]. Caffeine has the ability to protect against skin carcinoma as mentioned as a result of blocking of the ataxia telangiectasia and rad3-related (ATR) kinase [51]. No studies have yet proven the efficiency of caffeine in protecting against UVA.

Effect of Caffeine in Obesity

According to world health organization (WHO) and American medical association (AMA), Obesity is considered a chronic disease characterized by accumulation of fats or adipose tissues in different organs inside the body [52]. Obesity adversely affecting the functions of body organs which harms the whole body including skin [52]. Among the most common diseases associated with obesity are type 2 diabetes mellitus, metabolic syndrome, fatty liver disease, and different cardiovascular diseases [52]. In spite of all risks associated with obesity, its incidence was dramatically increased during the last 30 years [52]. "Globesity" is a term illustrating the increase in obesity globally, which reflects that our situation is really serious [53]. 38% of world's population are suffering from either being overweight or being obese, as mentioned by World Obesity Atlas in its 2023 report [53]. In 2030 it was predicted that the percentage of obesity in US adults will reach 78%, and in 2035 the percentage will reach 51% of the population all over the world [53]. Mortality rates increased as a result of obesity in 2019, 5 million obesity related deaths all over the world existed [54]. Even the global economy is at a crisis because of obesity costs, which is predicted to be increased in 2035 to reach 4 trillion US dollars, being comparable to the impact of coronavirus on global economy [53]. For all of these reasons, the FDA approved several medications with different mechanisms of action for treatment of obesity as Bupropion-naltrexone, Liraglutide, Orlistat, Phentermine-topiramate, Semaglutide, Setmelanotide, and Tirzepatide [55].

The whole world is turning towards the use of natural products for more sustainable, affordable, eco-friendly and clean way of treatment against many diseases. Lee, et al. [56] conducted a study that proved the efficacy of coffee ingestion in modestly lowering body mass index (BMI) a measure of overall adiposity, as well as waist circumference (WC) which is a measure of central adiposity [56]. Besides healthy food and physical exercise, coffee can help in lowering adiposity [56]. Another study was conducted by Tabrizi, et al. [57] and it demonstrated that impact of intake of caffeine on losing weight, BMI, and fat mass [57]. The study included thirteen randomized control trials with 606 persons [57]. The overall polled beta for caffeine intake was calculated and it was 0.29 (95%CI: 0.19, 0.40; Q = 124.5, I2 = 91.2%) for weigh, 0.23 (95%CI: 0.09, 0.36; Q = 71.0, I2 = 93.0%) for BMI, and 0.36 (95% CI: 0.24, 0.48; Q = 167.36, I2 = 94.0%) for fat mass [57]. On increasing caffeine intake twice, the reduction of weight, BMI, and fat mass increased two folds. According to Uner, et al. [58] caffeine has proved its ability in the treatment of obesity [58]. As they succeeded in preparation of caffeine solid lipid nanoparticles, using high pressure homogenization technique [58]. Poloxamer 407 was chosen as a surfactant and Compritol 888 ATO was used as solid lipid [58]. The optimal formula possessed particle size of 110.2 ± 0.1 nm and it proved its adipogenesis activity against 3T3-F442A cell lines [58].

Different Dosage Forms of Caffeine in Market

Caffeine is existing in many forms in the market as shown in (Figure 6) [59]. Caffeine used to exist as tablets or capsules, or it was drinkable as coffee, tea, or other drinks. Because caffeine is easily ingested, swallowed, and absorbed from the intestine, it is widely used in these forms [59]. Recent available forms of caffeine are gums, lozenges, bars, gels, and energy drinks. Nasal and mouth aerosols are the latest available dosage forms containing caffeine [59]. A wide range of dosage forms evolved as alternatives to the common dosage forms, with the aim of providing higher bioavailability, a quicker absorption rate, and subsequently more efficacy. Two studies were done to evaluate the effect of caffeinated bars and gels on athlete's performance as caffeine is very important for them for completion of their trainings. As a summary for the two studies, they mentioned that on athehete's administration of bars and gels enclosing caffeine in a dose of 100 mg, their cognitive functions, time to exhaustion as well as time trial performance were significantly. For more details and proper understanding, further studies should be done in this area [59]. As any orally administrated tablet, the action of caffeine tablets always appears after its administration by about 20 to 30 min, this time is consumed during its disintegration dissolution and then absorption. Caffeinated chewing gum offers a great advantage over ordinary caffeine tablets as it gives rise to very quick action because of immediate caffeine release from these gums. It was first invented for military use for giving a quick alertness action. A new form for administration of caffeine is mouth rinsing, it is considered a very effective way of caffeine administration as it gives rise to quick caffeine absorption [59]. The duration of mouth rinsing by caffeine for 5-20 s is considered a way of adenosine inhibition as it binds to its receptors present inside the mouth. Among the newest, very fast ways of caffeine delivery are caffeine nasal and mouth aerosols. Nasal caffeinated aerosols are very effective because caffeine possess very low molecular weight. Caffeine can therefore easily penetrate nasal membranes and it will be delivered quickly and easily to the brain. Caffeine mouth aerosols offer the advantage of delivering caffeine to the lungs directly and also to the heart giving rise to very quick action [59].

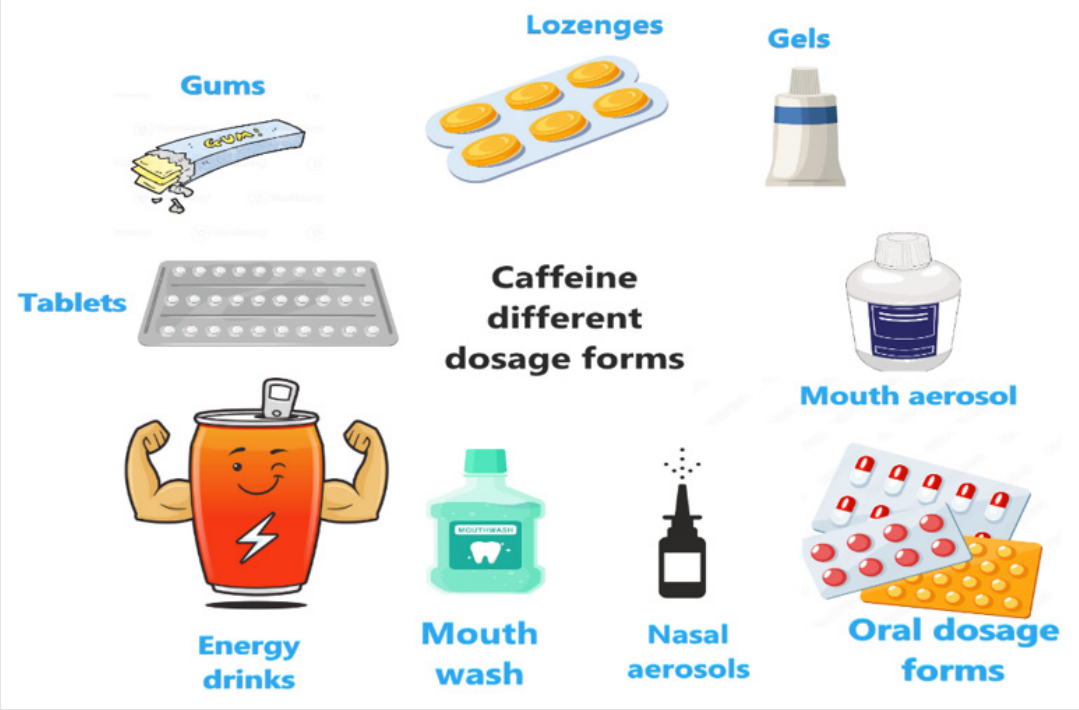


Figure 6: Different dosage forms of caffeine.

Adverse Effects Accompanied by Treatment with Caffeine Products

Many side effects are accompanied with the use of caffeine and they differ according to the dose consumed (60). Regarding to the side effects accompanied with low dose of caffeine are insomnia, and dependence which resulted in withdrawal symptoms as headache, hypertension, fatigue, drowsiness, stomach, and joint pain (60). Among side effects accompanied with excessive use of caffeine are vasoconstriction, hypertension, dehydration, bone loss, increasing gastric secretion, gastric motility, anxiety, colorectal cancer, restlessness, anxiety, palpitations, and glaucoma [60]. According to FDA, 2014 the huge

overdose of caffeine results in death and the LD50 (lethal dose 50%) of caffeine in humans is from 150 to 200 mg/kg [60]. The excessive use of caffeine during pregnancy give rise to many prenatal risks [60]. The world health organization has limited the daily consumption of pregnant woman for caffeine during the day to 300 mg only [61]. Caffeine excessive consumption during pregnancy adversely affects the fetus by several ways. In spite of easily crossing the placenta, caffeine is not metabolized easily by the placenta, the reason behind this is the absence of CYP1A2 isozymes [60]. Also, the fetus is not able to metabolize caffeine because of the lack of liver enzymes. Therefore, a subsequent accumulation of caffeine occurred in the systemic circulation of both the mother and her fetus. Fetal development is also adversely affected by excessive caffeine consumption. The reason behind this is the insufficient oxygen, nutrients, and blood supply to the fetus which affects his normal growth, and development [60]. This adversely affects the fetus's skeleton growth, induces abnormalities in their adrenal glands and its secretions, and give rise to low fetus weight due to intrauterine fetal growth retardation [60]. Different effects of caffeine intake in pregnant women and their fetuses are summarized in figure [60]. In spite of being very effective treatment for many dermatological conditions, the excessive use of caffeine containing skin products is not considered favored at all. Caffeine in high concentration may cause skin redness, stinging and even skin burn due to increasing blood circulation to the skin [62]. So mostly caffeine is added in topical preparations in a lower ratios about 3% only, to avoid its harmful effects [62]. Care also should be taken for pregnant women; they should not use caffeine topical products unless their physicians ask them to do. Excessive use of caffeine in pregnant women may give rise to early baby birth or babies with lower weight than normal [62].

Different Caffeine Nano Formulations

Being a polar substance with possessing low solubility in oil as well as water and hence less solubility and skin penetration the use of caffeine in cosmetics was limited [63]. So several researches were done on caffeine to increase its penetration into skin layers, bioavailability and hence its efficacy [60]. In 1994, Touitou et al succeeded in the preparation of caffeine liposomes, which are multiparticulate colloidal systems where one or more phospholipid concentric layers surround the aqueous medium [64], using a mixture of 20 % transcutol and 10 % oleic acid which was able to increase caffeine permeation into the skin by 40 more times [65]. The term "nanocosmetics" refers to narrowing the materials size to be less than 100 nanometer or the use of nanotechnology in cosmetics field [66]. It emerged to improve permeation, performance, bioavailability, and hence efficacy of skin products [66]. Several pieces of research were done on encapsulation of caffeine using different nanoformulations, such as nanoemulsions, microemulsions, silver and gold nanoparticles, solid lipid nanoparticles, copper oxide nanoparticles, nanoliposomes, nanohydrogel, nanocrystals, nanocapsules, and nanotubes [63]. For better physicochemical properties than liposomes, span 80 non-ionic vesicles were prepared giving rise to effective caffeine delivery for treatment of osteosarcoma in combination with chemotherapy [60].

Nanoemulsions are transparent submicron colloidal particles ranging from 20 to 500 nm [67]. The major components of nanoemulsions are aqueous phase, an oily phase, and an emulsifier [67]. The best method for transdermal delivery of caffeine is the nanoemuslion, because caffeine cannot penetrate lipophilic layers of skin so it can be enclosed in water in oil nanoemulsion for better skin delivery. Both caffeine nanoemulsions and microemulsions proved their efficacy in treatment of skin tumors [60]. In 2010 Shakeel, et al. [68] developed a method for caffeine nanoemulsion preparation intended for transdermal delivery of caffeine as an anticancer drug [68]. A significant increase in skin permeability of caffeine in using the nanoemulsion in comparison with aqueous caffeine solution [68]. In 2017, Af-iadh, et al. [69] used factorial design for the preparation of caffeine nanoemulsions, tween 80 and span 80 were used as surfactants, benzyl alcohol was used as an oily phase, and isopropyl myristate was used as a chemical penetration enhancer [69]. Caffeine's ability to penetrate the skin was done using in vitro franz diffusion cells using rat's skin [69]. The resulting nanoemulsion possessed particle size of 43 nm, PDI 0.572, and zeta potential of -0.2 mV, those particles appeared under TEM in a spherical shape [69]. Friere, et al. [70] 2019 prepared caffeine nanoemulsion for topical treatment of cellulites by testing skin permeation using in vitro franz diffusion cells [70]. The nanoemulsion was prepared using emulsification method using two surfactants oleth 3 and oleth 20 [70]. The nanoemulsion technique proved its ability in enhancement solubility and also stability of caffeine in production of cosmetics [70].

Solid lipid nanoparticles (SLN), are colloidal particles of size ranging from 50 to 1000 nm [71]. The major components of SLN are lipids, emulsifiers, co-emulsifiers, and water [71]. They should be non-toxic as well as biocompatible, highly stable, and highly bioavailable [72]. In 2015 Hamishehkar et al., were able to prepare caffeine solid lipid nanoparticles for the treatment of cellulites using Precirol® (lipid phase), and hot homogenization technique for the preparation [41]. In 2016 Puglia, et al. [73] prepared caffeine solid lipid nanoparticles by high speed homogenization using Softisan 100 as an oily phase, and poloxamer 188 as solid lipid [73]. The resulting nanoparticles showed a particle size range of 182.6 ± 8.4 nm, zeta potential of -32.3 ± 2.64 mV, and the drug loading percentage was 75% ± 1.1 (73). In 2018, Algul, et al. [74] were able to prepare caffeine solid lipid nanoparticles using homogenization as well as sonication techniques [74]. Caffeine was encapsulation efficiency into nanoparticles was 49.22%. The particle size of solid lipid nanoparticles were less than 210 nm, and its PDI were less than 0.3. Caffeine nanoparticles should initial burst in the first 3 min of in vitro release experiment and then it should controlled release for 6 successive hours [74]. Caffeine solid lipid nanoparticles efficacy in treatment of cellulites was confirmed by histological studies in rat's skin. In 2023 Kassem, et al. [42] succeeded in preparation of caffeine loaded nanostructured lipid carrier formulations which proved its efficacy in treatment of cellulites [42].

Nanocrystals give the drug many advantages including increasing its solubility, dissolution properties as well as bioavailability [75-77]. A study done was by Breuckmann et al., 2021 on the preparation of caffeine nanocrystals for topical administration [78]. They concluded that the prepared caffeine nanocrystals can penetrate hair follicles deeply on comparing it with caffeine solution giving rise to more absorption and hence bioavailability [78]. Methotrexate is a well-known, effective anti-cancer drug; unfortunately, it is immunosuppressive [79-81]. Hamed, et al. [79] 2023 succeeded in decreasing methotrexate immunosuppressive action by combining it with caffeine and folic acid loaded chitosan nanoparticles, which provided a promising treatment for many cancer types. The mean diameter, zeta potential, and PDI of the prepared nanoparticles was 140 ± 95.65 nm, 16.6 ± 3.46 mV, and 0.4 respectively [79]. Chitosan is a polymer used for preparation of chitosan nanoparticles because of being biocompatible, safe, and biodegradable [82-84]. Chitosan nanoparticles are very effective in encapsulating drugs and delivering them to specific body part [85-88]. Recently Hosny, et al. [89] loaded caffeine into chitosan nanoparticles to explore its effect on cardiovascular changes in obese rats [89]. They proved that caffeine loaded chitosan nanoparticles are very effective against different cardiovascular complications associated with obesity [89]. Mohammed, et al. [90] 2024 proved the efficacy of caffeine-loaded chitosan nanoparticles when accompanied with moringa leaf extract in the treatment of breast cancer [90]. The synergistic effect occurred between moringa extract as well as caffeine loaded chitosan nanoparticles showed a potent effect in anti-breast cancer as the mixture succeeded in downregulating oncogenic genes as (Her2, BRCA1 and BRCA2) [90-92].

Metallic nanoparticles are nanosized particles possessing a size range of lower than 100 nm and constituted from metals as silver, gold, iron oxide, copper, and nickel [93-95]. Metallic nanoparticles are commonly used nowadays because of its efficacy in cosmetic products, drug delivery, diagnosis, as well as treatment of many diseases [96,97]. Metallic nanoparticles offer many advantages including drug targeting, increasing drug's half-life and subsequently its bioavailability as well as efficacy [98,99], effective bio distribution of the drug, and also, offering high drug stability [99,100]. In 2017, Kamalakannan, et al. [101] succeeded in the preparation of caffeine-loaded gold nanoparticles using water in oil emulsification as well as solvent evaporation techniques [101]. Caffeine-loaded gold nanoparticles conjugated with PLA-PEG-PLA polymers proved their effective anti-inflammatory effect [101]. In 2021, khan et al prepared caffeine-loaded gold nanoparticles which were able to inhibit biofilms and persist cells of pathogenic bacteria [102]. Caffeine-loaded gold nanoparticles is a very effective antibiotic against many types of bacteria including both gram positive and gram negative ones [102,103]. Not only gold nanoparticles, but also CuO nanoparticles prepared using caffeine showed effective anti-bacterial action [104]. Mary, et al. [104] utilized the precipitation method in which caffeine acts as a stabilizer in different concentrations [104]. In 2020, Baghaienezhad et al prepared caffeine-loaded silver nanoparticles that proved its effective antibacterial action against both gram positive and gram negative bacteria [105].

In 2023, El-Desouky, et al. [106] fabricated eco-friendly silver-loaded nanoparticles using coffee waste extract, which proved its efficacy as a powerful antibacterial against many microbes [106]. The method used for preparation of such nanoparticles was simple, quick, without any harmful reagents and its duration was short that's why it is considered a promising way of silver nanoparticles preparation [106]. In 2023, Rasheed, et al. [107] were able to prepare caffeine loaded silver nanoparticles which act as a powerful antibacterial and also it had a positive impact on body minerals as calcium, magnesium, sodium, and zinc [107].

Conclusion

Caffeine has proven its efficacy for the treatment of several skin disorders, such as dark circles around the eyes, androgenic alopecia and hair loss, aging signs, wrinkles, cellulites, obesity, and skin cancer. Caffeine is available in the market in many dosage forms, including tablets and capsules. Recently, caffeine is available in the market as gums, lozenges, bars, gels, energy drinks, nasal, and mouth aerosols. In addition, mouth rinsing with caffeine is considered one of the new evolving methods instead of the traditional dosage forms with slow drug action and low bioavailability. The efficacy and activity of caffeine were improved by incorporating it into different nanostructures as they gave rise to better penetration into deeper skin layers. Among caffeine nano formulations are nano emulsions, solid lipid nanoparticles, nanocrystals, and metallic nanoparticles. Caffeine provides a sustainable, natural way for the treatment of skin disorders instead of the use of chemical drugs, which possess many adverse effects.

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