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Review Article

GREEN TEA CATECHIN LOADED NANODELIVERY SYSTEMS FOR THE TREATMENT OF PANDEMIC DISEASES

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ABSTRACT

Tea (*Camellia sinensis*, Family: Theaceae) is one of the extremely consumed beverages around the world, behind to water. The brew tea is the merely food product contains abundant quantity of the catechins. Green tea is the least processed and thus contains rich antioxidant, polyphenols, especially catechin called epigallocatechin-3-gallate (EGCG), which is whispered to be responsible for a wide range of the health benefits. The key to the amazing health benefits that are derived from green tea is that the leaves are steamed which preserves the EGCG compound from being oxidized. However, the other varieties of teas are under go fermentation process, which breaks down the potential EGCG and destroy from its healing properties. In reality, green tea has very extensive history dating back thousands and thousands of years ago. However, the pharmacological efficacy and stability of green tea catchiness are primarily depended on the formulation and way to drink to alleviate the deadly diseases with scientific evidence. Nanotechnology is a vibrantly emerging field especially in the pharmaceutical industry to explore a lot of application. The promising nano-delivery system used to enhance the therapeutic efficacy with a minimal dose, minimize the dose-related toxicity, target delivery, site-specific delivery, and controlled/sustain the delivery application. In recent decades, the application of nanotechnology has been utilized for phytopharmaceutical industry including green tea catechins to maximize the health benefits. In this review, we tried our level best retrieve the value of information on nanodelivery application of green tea catchiness for various devastating diseases.

Keywords: *Camellia sinensis*, Green tea, Catechine, Flavonoids, Nanoparticles, Nanoemulsion, Liposomes.

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INTRODUCTION

Since the ancient era, herbals and natural products are being used to devastate many deadly diseases including cancer, diabetes, cardiovascular complications, and psychological disorders. Unlike widely used modern medicine, herbal formulations have numerous vital phytoconstituents that all work simultaneously to eradicate the diseases [1-4]. However, the health benefits of herbal medicines not extensively delivered to heal the diseases due to deprived acceptance by many physicians, and lack of scientific and clinical evidence [5-7]. The majority of the phytoconstituent before get absorbed into the systemic circulation, deactivated by a wide range of gastrointestinal pH, biological enzymes, and liver metabolism [8-10]. Consequentially, the optimum therapeutic outcome of herbal drugs may not attain. If the drug does not achieve the optimum concentration to the affected region at "minimum effective level," then there will be no therapeutic outcome of the drug. During recent decades, nano drug delivery technology has been utilized for a wide range of pharmaceutical compounds to deliver sustains or controlled manner to treat various chronic illness [11]. After successful preclinical and clinical research, numerous nanoformulations have been existed to alleviate various chronic illness and cosmetic applications [12,13].

Tea (*Camellia sinensis*, Theaceae) is one of highly consumed beverages around the globe [14-17]. In addition to being the most widely consumed tea, it is the only food product known to contain substantial levels of the catechins [18,19]. All tea plants belong to the same species *C. sinensis;* but local growing conditions (altitude, climate, and soils) vary, resulting in a multitude of distinctive leaves [20,21]. The way the leaves are processed, however, is even more important in developing the individual characteristics of the three predominant types of tea: Green, black, and oolong. Green tea is the least processed and thus contains rich antioxidant, polyphenols, remarkably a catechin called epigallocatechin-3- gallate (EGCG), which is believed to be accountable for most of the health benefits [22-26]. The following catechins are abundantly present in green tea including (-)-EGCG (~ 59% from total catechins); (-)-EGC (~19% from total catechins); (-)-epicatechin (EC)-3-gallate (~14% from total catechins); and (-)-EC (6% from total catechins). It also carries gallic acid and other phenolic compounds including chlorogenic acid and caffeic acid, and flavonols such as myricetin, kaempferol, and quercetin [27]. Green tea is made by steaming the fresh leaves, rendering them soft, pliable, and preventing them from fermenting or changing color [28,29]. After steaming, the leaves are rolled, then spread out and dried with hot air until they become crispy. The resultant tea has greenish-yellow in color, slightly astringent flavor. Green tea is extremely famous beverage in all around the world. It not only captures the taste, aroma and color of spring but also delivers this delightful bouquet along with the highest concentration of beneficial phytoconstituents and the low level of caffeine compared to all other teas [30-32]. The key to the amazing health benefits that are derived from consuming green tea is that, the leaves are steamed which preserves the EGCG compound from being oxidized [33,34]. Other varieties of teas are fermented but which rupture the vital compound EGCG and spoil its healing ability. In fact, green tea has very long historical background since few 1000 years ago.

Nanoparticle is an emerging drug delivery system which has applied to the vast majority of herbal phytoconstituents to attain greater therapeutic efficacy [35,36]. These delivery systems have widespread advantages including enhanced drug loading, protect against gastrointestinal pH, escape form first-pass metabolism, ability to achieve prolonged release, and improved stability [37-39].

Encapsulation of herbal extracts into nanocarrier system has certain added advantages embrace with sustain/controlled drug release, site-specific drug release, improved enzymatic stability, and increased intracellular drug release [40-43]. We have done extensive literature review on the health benefits of catechin from green tea extract (GTE) and their pharmaceutical and biological challenges toward achieve maximum therapeutic potential and also enlighten the application of nano drug delivery utilized to improve its pharmacological and pharmaceutical attributes.

CHALLENGES OF DEVELOPING GREEN TEA CATECHIN AS THERAPEUTIC AGENT

Bioavailability challenges

A major challenge in extrapolate the therapeutic activities of green tea polyphenols *in vitro* to possible effects *in vivo* bioavailability [44]. The deprived bioavailability of EGCG might be attributed to several factors: (a) The instability of EGCG in alkaline or neutral condition, (b) low cellular uptake due to high aqueous solubility and poor hydrophobicity to cross cell membrane; (c) metabolic transformations such as methylation, glucuronidation and sulfation [21], and (d) active efflux effect of many polyphenolic compounds by the Multidrug Resistance-Associated Protein 2 [45-50]. Administration of decaffeinated green tea to the rats, the plasma bioavailability of EGCG, EGC, and epicatechin EC was 0.1%, 14%, and 31%, respectively, compared with mice model, whose absolute plasma bioavailability of EGCG was 26.5% [51]. Numerous researches on the pharmacokinetic profile of tea polyphenols in humans have been reported till date [52-55]. The oral administration of green tea at dose 20 mg/kg body weight resulted in plasma C_{max} for EGCG at 78 ng/mL; it was very low to the micromolar concentration usually required for *in vitro* activity. Thus, the extent of bioavailability and therapeutic efficacy of GTE primarily depends on the route of administration and site of the organ [56-59].

Biological stability of GTE

The EGCG is unstable phytoconstituent which is effortlessly prone to oxidation reaction. The researcher Friedman reported that EGCG on green tea showed a decrease in EGCG concentration after stored at the dry condition at 20°C during 6 months due to the oxidation process [60]. TCs as a mixture in alkaline solutions (pH > 8) were highly unstable and degraded almost completely within a few minutes, whereas in acidic solutions (pH < 4) it was highly stable. From the pH 4–8, the stability of GTCs was pH-dependent, i.e., the lower the pH, the greater, the stability. Four EC isomers demonstrated varying stability in alkaline solutions with EGCG and EGC being equally instable, and EC and ECG being relatively stable [61-64].

Stability issues during green tea processing

It is well documented that polyphenol exists in tea is responsible for health-related beneficial effects. The content and stability of the tea polyphenols mostly depend on several production parameters including vascular plant, harvesting season, age of the plant, environmental condition, and process condition. It is well documented that process condition is one of the vital factors that determine the quality of the tea product [65].

On the other hand, EGCG is unstable to light and warm condition. The degradation temperature for EGCG is 85°C while exposed to radiation for 1 h. Therefore, infundation extraction method should be performed in extreme cold condition and the pH is adjusted to 4 using phosphoric acid [66]. This treatment could increase EGCG concentration much higher in methanolic solution, while the green tea after infundation process that underwent the temperature decreasing process until 22°C showed that EGCG concentration was 30% lower than methanol. Green tea that underwent 90°C infundation method during 30 min without pH alteration exhibited similar to methanolic solvent. This study reported that the importance of extreme decreasing temperature and decreasing pH to 4 after infundation process and the resultant EGCG concentration was 6.7% [67]. Prayong *et al*., 2007, reported that the EGCG concentration was 0.21–9.63% [68], whereas the EGCG concentration end in brewed tea was 2.8–3.96% [69]. Besides that, EGCG concentration with extreme decreasing temperature and adding phosphoric acid till pH 4 was 35% [70]. The second most abundant flavonoid present in green tea leaves is catechin. Tea catechins undergo degradations and epimerization in the aqueous condition during thermal processing. It is known that thermal degradation and epimerization of green tea catechins follow pseudo-first-order reaction kinetics in the aqueous solvent system [71].

NANO DRUG DELIVERY APPROACH OF GREEN TEA

EGCG offers enormous health benefits since it is ample accessible and inexpensive to extract and isolate from the tea leaf; it may be administered orally and proven safety profile. The usage of EGCG in clinical practice was greatly hampered due to diminutive half-life, short stability, and less bioavailability [71]. The stability issues of orally ingested EGCG were evidenced that the detected plasma concentration was recorded very poor (0.2–2%). In addition, the effective antitumoral concentration of EGCG *in vitro* is generally an order of magnitude higher than the levels measured *in vivo*, which restricts its effectiveness [72]. Moreover, EGCG has poor target specificity. Therefore, a technique that will increase the EGCG stability, bioavailability, and cell-specific delivery is highly important to attain maximum therapeutic efficacy. Recently, the nano delivery technique was introduced to enhance the pharmacokinetic and pharmacodynamic of the efficacy of chemotherapeutic agents to inhibits, slow-down, or revert the cancers. The encapsulation of EGCG into a specific nanocarrier can increase its solubility and bioavailability, protect it from premature degradation, provide prolonged circulation time and induce higher levels of target specificity [73-76]. Polymeric nanoparticles have a promising delivery system in the field of the biomedical field due to its biocompatibility, biodegradability, possibility to control the rate of polymer degradation and release rate, mechanical strength, and high structure versatility [77,78]. With these positive prospects, the various polymeric nanoparticulate drug delivery systems have been developed and investigated to enhance the therapeutic potential of green tea polyphenols. In this review paper, we tried our level best to extract and compiled the most vital information related to the nano delivery and its application toward green tea polyphenols.

Chitosan nanoparticles (CSNP)

Catechins found in tea leaf have gained significant attention as a result of their favorable pharmacological properties including cardioprotective, neuroprotective, and anticancer effects [79]. However, their therapeutic prospects are hampered due to their deprived oral bioavailability, poor stability, and intestinal absorption. To enhance the oral bioavailability, (+)-catechin (C) and (-)-EGCG were encapsulated into CS-NP drug delivery system. Victimization excised mouse small intestine in victimization chambers, encapsulation considerably increased ($p<0.05$) internal organ absorption. The additive amounts transported after encapsulation were significantly higher, i.e., 302 versus 206 ng/cm and 100 versus 58 ng/cm for C and EGCG, respectively. The mechanism of enhanced absorption was not through an impact of CS-NPs on internal organ either paracellular or transcellular transport mechanism. However, it was possible as a result of the stabilization of catechins after encapsulated into CSNP [80]. The researcher Alotaibi *et al*., 2013, also encapsulated EGCG into Poly (lactic-co-glycolic acid) (PLGA) based polymeric nanoparticles and investigated the effect of DNA damage against lymphocytes of healthy and colorectal cancer patients pretreated with oxaliplatin of satraplatin. The obtained results concluded that the PLGA encapsulated EGCG significantly intensified DNA damage levels in a dose-dependent manner. In contrast, free EGCG promoted a reduction in DNA damage [77].

Solid lipid nanoparticles (SLN)

Manea, Ana-Maria *et al*., 2014, developed GTE loaded SLN by high shear homogenization technique and investigated the antioxidant potential and antimicrobial activity. The antioxidant efficacy of GTE loaded SLNs, was higher than free-SLNs or GTE in bulk as a result of a synergistic effect between the complex structural lipid matrix and bioactive GTE

encapsulated. The use of the two surfactants Tween 20 and Tween 80, as well as two different concentrations of GTE (0.1 and 0.17%), and did not produce any significant variation. The highest antioxidant (99.6%) was obtained when Tween 20 was used as a surfactant and the concentration of GTE (0.17%), while the less antioxidant (87.3%) was exhibited when Tween 80 used as a surfactant and the concentration of GTE was 0.1% [81].

Green tea catechins constitute about 8–15% of total dry tea weight. The most abundant catechin is EGCG, which accounts for 25–55% of total catechins. One cup of green tea made using a 2.5 g tea bag contains about 100 mg of EGCG [82,83]. Consumption of EGCG has been reported to have several health benefits including antioxidant, anti-inflammatory, anti-tumorigenic, and antiangiogenic properties as established by Chyu *et al*., 2004 [84].

De Pace *et al*., 2013, developed EGCG loaded into liposomes and chitosan-coated liposomes, with the vesicular size ≤100 nm in diameter to enhance the stability. The nanoliposomal delivery system has been drastically enhanced the stability of EGCG in both phosphate-buffered saline and Eagle's minimum essential (EME) cell culture medium. The free EGCG in EME medium was completely degraded after 8 days at 4°C. However, EGCG loaded liposomes and chitosan-coated liposomes were degraded 62% and 38%, respectively, at the same conditions and initial concentrations. After 1-h incubation at 37°C, the EGCG degradation rates of 0.5 mM of free EGCG, EGCG loaded liposomes, and chitosan-coated EGCG loaded liposomes in EME medium were 100%, 46%, and 32%, respectively [85].

It is well established that EGCG has not readily absorbed in humans and animal models. The Barras *et al*., 2009, had conducted the pharmacokinetic and bioavailability investigation of tea leaf catechins using rat models. The plasma peak concentrations of green tea catechins exhibit at 2–4 h after oral administration. The absolute bioavailability of EGCG after intragastric administration of decaffeinated green tea is about 0.1% in rats [86]. Consistent with this result, the bioavailability of EGCG is 0.14% in males and females after consumed tea which contains 400 mg catechins for 24 h period. The peak plasma EGCG concentration is around 0.15 μM after drinking two cups of green tea. A majority of published cell culture studies have used EGCG at physiologically irrelevant concentrations in the range of 10–200 μM. Since EGCG at lower, and physiological relevant (achievable by oral administration) concentrations have little or very limited efficacy and thus, it is highly important to enhance the EGCG bioavailability, and the nanoparticulate drug delivery technology appears to be an appropriate concept to address these issues [87]. In fact, numerous researches revealed that nanoencapsulation system has been one of the prominent nano delivery systems which significantly increases EGCG stability and improves drug release rate, which partially contributes to the increased cellular uptake of EGCG. In another research reported that the chitosan-based nanoparticulate systems have capable to enhance the EGCG bioavailability [87-90]. Dube *et al*., 2013, compared the intestinal absorption of free EGCG and nano-EGCG (CSNP) using excised mouse jejunum. They added 50 μM of free and nano-EGCG in the mucosal chambers and collected the transported EGCG in the serosal chambers after 3 h time interval, and found that nano-EGCG had about two-fold higher accumulative transported than free EGCG. The enhanced stability of EGCG and improved transcellular transport process was achieved in nanoparticle system, but not paracellular transport mechanism, may partially contribute to the enhanced intestinal absorption [91]. After reaching the apical membrane of intestinal epithelial cells, most of the nanoparticles cross enterocytes through transcellular transport mechanism. Nanoparticles are internalized into enterocytes and then transported across enterocytes. The particle size ≤500 nm in diameter is internalized through both clathrin- and caveolae-mediated endocytosis. The process of endocytosis can be enhanced by modifying nanoparticles, for example, by coating with polyethylene glycol or positive charges on the surface of nanoparticles [80]. The researcher Dube *et al*., 2013, measured the plasma concentrations of EGCG in mice after oral administration of either free EGCG or EGCG encapsulated CSNP. Compared to free EGCG, EGCG-loaded CSNP increased plasma EGCG concentrations by a factor of 1.5 [46]. EGCG nano lipidic particles increased the oral bioavailability by ≥2 folds as compared to free EGCG in rats as documented by Wang *et al*., 2013 [87].

Gold nanoparticles for tumor targeting

The tea based gold nanoparticles (T-AuNPs) [93] have evidenced remarkable *in vitro* stability in various buffer solution including saline, histidine, HSA, and cysteine solutions. T-AuNPs with phytochemical coatings have shown important affinity toward prostate (PC-3) and breast cancer (MCF-7) cells. This study reported on the cellular acquisition of T-AuNPs through endocytosis into the PC-3 and MCF-7 cells. The T-AuNPs follows all principles of green chemistry and are found to be non-cyanogenic as evaluated by MTT assays. This true biogenic green nanotechnological process T-AuNPs paving excellent opportunities for their applications in molecular imaging and clinical therapy [94].

Several reports have described the results of gold NPs in conjugation with EGCG for cancer treatment. The AuNPs loaded with EGCG (EGCG-pNG) prepared by ultrasonication technique and investigated their effect in the treatment of bladder cancer both *in vitro* and *in vivo* [95]. Their results shown that this strategy induced high levels of cytotoxicity in bladder cancer cells (MBT-2) without affecting the viability of normal cells (Vero cells). Treatment with EGCG-pNG was shown to induce apoptosis through triggering the intrinsic apoptotic pathway through the activation of caspases-3 and caspases-7 and these were confirmed by *in vivo* studies. C3H/HeN mice subcutaneously implanted with MBT-2 cells revealed significant higher reduction in tumor volume after oral ingestion of EGCG-pNG in comparison with free EGCG. In addition to this, nanoparticles were also administered through intratumoral and intraperitoneal route. These routes of administration were more effective than oral administration in suppressing tumor growth. The *in vitro* results showed that gold NPs induced nearly five-fold higher levels of apoptosis in B16F10 murine melanoma cells compared to non-encapsulated EGCG. The *in vivo* results demonstrated that intratumoral injection of EGCG NPs induced a reduction in the tumor volume of a mouse melanoma model compared with the control group. This ability to inhibit tumor growth was 1.6 times higher when EGCG was encapsulated compared to free EGCG [95].

PLGA/PEG nanoparticles

The EGCG encapsulated with polylactic acid–polyethylene glycol nanoparticles and found that encapsulated EGCG retains its biological effectiveness with over 10-folds dose. The advantage for exerting its proapoptotic and growth suppressive effect, critically important determinants of chemopreventive effects of EGCG in both *in vitro* and *in vivo* systems. Hence, this study could serve as a basis for the use of nanoparticle-mediated delivery to enhance bioavailability and limit the toxicity of chemopreventive agents, such as EGCG [73].

Nanospheres for bioavailability enhancement

Nano BioSpheres Delivery System produced by the proprietary method, they are taken up more readily by cells than larger particles. Nanospheres are very small particles, measured in nanometers (nm), or billionths of a meter, that are now burgeoning into nutrient-delivery systems with diameters as small as 50 nm or even lower. Those showing greater efficacy are made of natural lipids, in which lipophilic compounds, such as the nutrients mentioned above, can readily dissolve [96].

Liposomes

Liposomes are vesicular drug delivery system forming a membrane-like phospholipid bilayer enclosing an aqueous compartment. This vesicular delivery system facilitates to encapsulate both lipophilic and hydrophilic drugs with higher concentration. In addition, liposomes are biodegradable and present minimal levels of toxicity due to the biodegradable nature of the phospholipid membrane [97,98]. Fang *et al*., 2006, developed liposomes with EGCG for topical and intratumoral

delivery to treat BCC (basal cell carcinoma) in female nude mice. The authors concluded that intratumoral injection of liposomes was the most effective route to succeed in cancer cells, promoting an excellent quantity of EGCG deposition in neoplastic cells. The same research group has also reported the applications of liposomal formulations for BCCs treatment *in vivo* after intratumoral administration. According to the authors Fang *et al*., 2006, that the nanoencapsulation of EGCG significantly increased the stability as compared to free drug, which may indicate that liposomes protect EGCG against oxidation and degradation. The synthesized liposomes also enabled higher EGCG accumulation in tumor tissues and induced higher levels of BCC cell death compared to the non-encapsulated EGCG treatment at lower concentrations [99].

Rashidinejada *et al*., 2014, encapsulated tea catechin and EGCG in soy phospholipid liposomes was examined at four different concentrations (0%, 0.125%, 0.25%, and 0.5% w/v), and inclusion in cheese at 1/3 and 0.25% w/v. The empty capsules had a mean diameter of 133 nm and considerably ($p<0.05$) enlarged with the addition of catechin or EGCG. The microscopical investigation disclosed the lamellae and central core of the liposome and addition of antioxidants gave a big ($p<0.05$) increase within the size of liposomes. Liposome's had zeta potentials value in the range between −42.4 and −46.1 mV with no vital distinction between treatments, suggesting stable vesicle systems. High potency (>70%) and yield (~80%) were achieved from the incorporation of catechin or EGCG within the vesicle structure [100].

Phytosomes

A phytosome is class of vesicular delivery system utilized to encapsulate the herbal extracts or isolated active principles with a phospholipid bilayer system used to administer both topically as well as orally. To overcome the low bioavailability and poor oral absorption of EGCG, Kazi Kazi *et al*., 2016, had formulated the catechin loaded nano phytosomes, newly acquainted forms of herbal formulations, with better bioavailability, entrapment efficiency, and stability using quality by design approach [101]. Catechins were extracted from green tea leaves using an aqueous solvent system at various temperature conditions. The concentration of EGCG in the extracted catechins was determined using ultra-performance liquid chromatography (UPLC) method. The obtained result from UPLC showed that 500 µg/ml EGCG was present in GTE. Particle size distribution data showed that phytosomes were in the range of 130–270 nm when characterized using Malvern Zetasizer and microscopic method. The rate and concentration of phospholipid were identified as critical process parameters and critical material attributes, respectively, affecting the quality attributes of phytosome. Formulations which proceeded at high addition rate exhibited smaller particle size and PDI compared to the formulations with low addition rate. The concentration of phospholipid has not influenced the particle size of phytosome at buffer pH 5.5, while the increased concentration of phospholipid and buffer pH 7 the particle size was decreased. The entrapment efficiencies for phytosome were in the range of 63–86%, which was related to the size of the phytosomes. This study concluded that the phospholipid concentration and addition rate have marked an impact on average particle size, PDI, and encapsulation efficiency of nano phytosomes [101].

Protein (oligomer) based nanoparticles

IBN nanotechnology researchers have designed a therapeutic nanocarrier for drug delivery using novel compounds derived from EGCG. The core of this carrier is made of an oligomer of EGCG (OEGCG), which can encapsulate drugs and proteins, such as Herceptin, a protein drug currently used to treat breast cancer. Polyethylene glycol (PEG)-EGCG was used to form the shell of this carrier. This novel compound is constituted of PEG, which is a known "stealth" polymer which acts to increase the circulation time of the carrier system, preventing it from being detected and filtered out of the body by the immune system before it reaches the tumor cell [102]. Micellar nanocomplexes (≤100 nm in dimension) are formed from the OEGCG core and PEG-EGCG shell, protecting the protein drug from rapid proteolysis and renal clearance, while providing for tumor targeting. The research group conducted preclinical studies to evaluate the performance of IBN's green tea-based protein delivery system [103]. The study revealed that IBN's green tea nanocomplex loaded with Herceptin reduced tumor growth much more effectively when compared to administering Herceptin on its own. Using this nanocarrier, two-fold drug accumulated in the cancer cells, indicating an improved tumor targeting ability. At the same time, the drug accumulation in the other organs (liver, kidney, and lung) was lowered substantially. Green tea-based nanocarrier, in which the carrier itself displayed the anticancer effect, can boost the cancer efficacy when used together with the protein drugs. Author Motoichi Kurisawa developed green tea based nanocarrier drug delivery system to eradicate cancer and he had filed a patent for his formulations. The green tea-based micellar complexes are also being examined for the delivery of active ingredients in personal care and nutritional products [104].

Nanoemulsion system

Nanoemulsion is a suitable delivery system for nutrients to improve bioavailability by enhancing internal organ uptake. Kim *et al*., 2013, had established the inhibitory and hypolipidemic effects of nanoemulsified green tea extract (NGTE). The inhibitory effect was measured by a pair of 2′-azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS) radical scavenging assay and dichlorofluorescein diacetate (DCFH-DA) assay. C57BL/6 mice were fed an impression high-fat diet, GTE, or NGTE diet for 4 weeks. In composition analysis, GTE and NGTE contained similar total catechin concentrations. The antioxidative impact of GTE was comparable that of NGTE within the ABTS assay, GTE had a marked impact, though NGTE was more practical than GTE within the DCFH-DA assay within the mouse feeding experiment, total and low-density lipoprotein cholesterin concentrations were considerably reduced when NGTE treatment as compared with GTE treatment in high-fat-fed C57BL/6J mice over the course of 4 weeks. The hypocholesterolemic effects were larger within the NGTE cluster compared with the GTE cluster (24% vs. 15.4% cholesterol reduction compared with the control). Expression of 3-hydroxy-3-methylglutaryl coenzyme enzyme was considerably down-regulated. Super molecule expression of beta-lipoprotein receptor was considerably enlarged within the livers of each the GTE- and NGTE-treated groups (+234.1%, $p<0.01$ and +274.7%, $p<0.001$), with a larger impact within the NGTE than within the GTE groups. These results suggested that nanoemulsion technique considerably promote the hypocholesterolemic efficacy of GTE *in vivo* attributable to enhance bioavailability [105].

Liquid crystalline nanocomposite

A liquid crystalline system (LCS) is a kind of nanostructured system accustomed incorporates various bioactive. Liquid crystals are identified since 1889, once Lehmann represented AN intermediate state within the thermal transformation from solid to liquid state. Hence, a striking approach to beat this downside to safeguard the GTE is its incorporation into LCS and these drug delivery systems with completely different rheologic properties, since LCS have each fluid-liquid and crystalline-solid property. The *in vivo* inflammation assay disclosed that the less elastic and consistent LCS, F25E, and F32E given statistically constant medication activity compared to the positive management, decreasing considerably the paw swelling when 4 h; whereas, the foremost structured and elastic LCS, powerfully restricted the potential effects of GTE. Thereby, the event of drug delivery systems with appropriate rheologic properties might enhance GTE bioavailability; sanction its administration through the skin for the treatment of inflammation [106].

Lipid nanoparticles for cosmetics

In year 2007, Grassland launched the supermolecule mainly based nanoparticles of Swiss cellular white illuminating eye essence. Swiss cellular white intensive ampoules that contain tea leaf extract, glycoprotein, herb root extract, horsetail extract, and viola extract [107].

CONCLUSION

Even though the health benefits of tea products are famed for thousands of years, basic analysis findings on its main phytoconstituent, EGCG, have

well researched to be extraordinarily promising in various therapeutic benefits within the past decades. Moreover, the current data revealed that peoples from United States drinking large amounts of tea, or taking over-the-counter green tea extract product for desirable health benefits. From this review paper, we able to concluded that the potent EGCG has exposed to various nano drug delivery systems to improve the stability, rate of absorption and bioavailability. The polymeric nanoparticles, lipid-based nanoparticles, the vesicular system including liposomes, and phytosomes were adopted to develop green tea based products especially EGCG compound. The numerous health edges of EGCG as a prophylactic, however conjointly as a therapeutic, agent acting through totally different pathways are well documented within the literature. The conflict between *in vitro* and *in vivo* studies could also be thanks to its erratic bioavailability. Aspects regarding these facts, however conjointly with reference to dose levels, administration frequency and potential aspect effects stay to be addressed in future clinical trials.

AUTHORS' CONTRIBUTIONS

Satheesh Babu Natarajan, Suriyakala Perumal Chandran, Anjaneyulu Vinukonda, and Senthil Rajan D. have equally contributed for thematic preparation and editing of the manuscript.

CONFLICTS OF INTEREST

The authors declared that there are no conflicts of interest.

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