Chlorogenic acid: Potential source of natural drugs for the therapeutics of fibrosis and cancer

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ABSTRACT

Fibrosis and cancer is described by some epidemiological studies as chronic stages of different disease conditions typically characterized by uncontrolled accumulation of extra-cellular matrix (ECM), thereby leading to inflammation of tissues and organ (lungs, heart, liver and kidney) dysfunction. It is highly prevalent, and contributes to increased mortality rate worldwide. Currently, the therapeutical approaches involving selected medications (bemcentinib, pirfenidone and nintedanib) obtained synthetically, and used in clinical practices for fibrosis and cancer management and treatment has shown to be unsatisfactorily, especially during progressive stages of the disease. With regards to finding a more potent, effective, and promising curative for fibrosis and cancer, there is need for continuous experimental studies universally. However, phytochemical constituents’ particularly phenolic compounds (Chlorogenic acid (CGA)) obtained from coffee, and coffee beans have been predominantly utilized in experimental studies, due to its multiple pharmacological properties against various diseases. Considering its natural source alongside minimal toxicity level, CGA, a major precursor of coffee have gained considerable attention nowadays from researchers worldwide, owing to its wide, efficacious and beneficial action against fibrosis and cancer. Interestingly, the safety of CGA has been proven. Furthermore, numerous experimental studies have also deduced massive remarkable outcomes in the use of CGA clinically, as a potential drug candidate against treatment of fibrosis and cancer. In the course of this review article, we systematically discussed the beneficial contributions of CGA with regards to its source, absorption, metabolism, mechanistic effects, and molecular mechanisms against different fibrosis and cancer categorization, which might be a prospective remedy in the future. Moreover, we also highlighted CGA (in vitro and in vivo analytical studies) defensive effects against various disorders.

Introduction

Some analytical and clinical investigations stipulates that fibrosis and cancer intertwine and share distinctly overlapping characteristics. With respect to injury (deregulated response) that occurs in all tissues of the body, fibrosis is indicated via immune cells and fibroblast activation, contributing to continuous inflammation and deposition of extracellular matrix (ECM). Cancers are usually driven through genetic alterations emanating from dissemination, dysregulated cell survival, and proliferation. In addition, non-cancerous constituents of malignant tissues such as ECM, inflammatory cells, and fibroblasts play significant roles in progression of cancer, and oncogenesis by yielding a pro-mutagenic surrounding where cancer cells could thrive, contributing to their invasiveness, survival, and growth. Fibrosis and cancer are reportedly known to possess similar pathophysiological pathway commonalities involving inflammation, cellular senescence, epithelial mesenchymal transition (EMT), hippo mechanism activation, ECM modification, genetic alterations, TGF-β overproduction, fibroblast proliferation and differentiation, elevating invasiveness and stiffness respectively [1–6]. Numerous causative risk factors such as diet, excessive alcohol consumption, smoking tobacco, genetic predisposition, radiation, and reproductive behavior, occupational and environmental pollutants (asbestos fibers, dust, silica, birds and animal droppings) are considered to be associated with fibrosis and cancer in human population [7–15].

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As reported by World health organization (WHO), fibrosis and cancer, still remains one of the leading cause of deaths affecting millions of individual universally. Currently, the therapeutical approaches involving selected medications (bemcentinib, pirenfedone and nintedanib) obtained synthetically, and used in clinical practices for fibrosis and cancer management and treatment has shown to be unsatisfactorily, especially during progressive stages of the disease [16–23]. With regards to finding a more potent, effective and promising curative for fibrosis and cancer, there is need for continuous experimental studies universally.

However, phytochemical constituents particularly phenolic compounds (Chlorogenic acid (CGA)) obtained from coffee and coffee beans have been predominantly utilized in experimental studies, due to its multiple pharmacological properties (anti-metastatic, anti-oxidative, naphthoantracycline, anti-diabetic, anti-hypertensive, hepatoprotective, anti-bacterial, neuroprotective, anti-proliferative, central nervous system stimulator, anti-obesity, cardioprotective, anti-pyretic, anti-viral, anti-angiogenic etc.) against various diseases forms [24–39]. Considering its natural source alongside minimal toxicity level, CGA, a major precursor of coffee have gained considerable attention nowadays from researchers worldwide, owing to its wide, efficacious and beneficial action against fibrosis and cancer [40, 41]. Interestingly, the safety of CGA has been proven [42, 43]. Furthermore, numerous experimental studies have also deduced massive remarkable outcomes in the use of CGA clinically, as a potential drug candidate against treatment of fibrosis and cancer.

In the course of this review article, we systematically discussed the beneficial contributions of CGA with regards to its source, absorption, metabolism, mechanistic effects, and molecular mechanisms against different fibrosis and cancer categorization, which might be a prospective remedy in the future. Appropriate databases and archives like Embase, Hindawi, Springer, Google scholar, and PubMed etc., were applied in this literature.

Chlorogenic acid

Source, absorption and metabolism

Chlorogenic acid (CGA), otherwise known as 3-cafeoylquininate (3-CQA) or chlorogenate is a biologically active polyphenolic compound that represents an entire ester-hydroxycinnamic and quinic acid group involving dicaffeoyl, caffeoyl, coumaroylquinic and feruloyl acids respectively [44]. It portrays numerous therapeutical effects and properties such as minimal oral absorption rate and soluble in ethanol and acetone. Table 1 highlights the CGA (in vitro and in vivo analytical studies) defensive effects against other various disorders or conditions. Notably, most authors nowadays still have misconception regarding CGA (Fig. 1), due to its nomenclatural divergences [45–47]. CGA is usually marketed as svetol, widely obtained and distributed in herbs, foods, dicotyledonous ferns and plants species namely berry fruits, tea, apple, cocoa, coffee, citrus fruits, roasted bean, pears, carrots, wormwood, artichoke, potatoes, eggplant, betel, kiwi fruits, tobacco leaves, burdock, eucommia, coffee beans, tomatoes, honeysuckle, and grapes [48–56]. With regards to its health boosting attributes, CGA is also significantly applied clinically, particularly against fibrosis and cancer and serves as the main constituent in traditional herbal medicine (THM) formulations for detoxification, and heat clearance [57–61]. Furthermore, the excretion, utilization and bioavailability of CGA is still yet unclear. In humans, around one-third of chlorogenic acid ingested are absorbed via the small intestine, whereas absorbed in the stomach of mice through prototype [62–65]. Following absorption, CGA is further metabolized into metabolites of sulfate, glycosides and glucuronic acid.

Mechanistic actions of CGA on fibrosis

A great number of experimental studies conducted by most researchers for over a decade has revealed positive significant actions of CGA use against treatment of chronic disease conditions such as fibrosis. Table 2 outlines the pharmacological activities (including assay models and signaling pathways) of CGA in various forms of fibrosis.

Chlorogenic acid and liver fibrosis

Liver fibrosis is described as uncontrolled deposition of ECM in liver tissue that leads to its functional and structural changes [104, 105]. It is mainly caused by various factors involving nonalcoholic steatohepatitis (NASH), autoimmune hepatitis, cholestatic liver disease, alcohol consumption, nonalcoholic fatty liver disease (NAFLD), and viral hepatitis [106]. Liver fibrosis still remains a significant health issue globally. Numerous studies by researchers regarding CGA potency on liver fibrosis has been reported and also continuously ongoing. Fig. 2 shows the diagrammatic illustration for the mechanistic effects and signaling pathways of CGA in ameliorating liver fibrosis.

CGA hampers liver fibrosis via obstructing the miR-21-regulated Smad7 or transforming growth factor beta-1 (TGF-β1) or interleukin-13 (IL-13) mechanism [90, 91]. CGA defends against CCL4 triggered liver fibrosis (in-vitro and in-vivo) via suppression of the oxidative stress [92], activation of HSCs and the production of vascular endothelial growth factor (VEGF) and TGF-β1 [93]. In addition, CGA diminishes fibrosis and inflammation via suppression of toll-like receptor 4 (TLR-4) mechanism [94]. CGA also exerts protective actions on fibrosis in nonalcoholic steatohepatitis through down-regulating multiple pro-fibrogenic factors and oxidative stress via HIF-α/miR-122 and Nrf2 pathways respectively [95]. Collectively, CGA prevents the oxidative stress, inflammation, and fibrosis in HSCs and fibroblast cells during liver fibrosis through inhibition of miR-21/Smad7/TGF-β1/IL-13/TLR-4/HIF-α/miR-122 and Nrf2 signaling pathways.

Chlorogenic acid and other fibrosis

The capability and efficacy of CGA could also be indicated in other fibrosis forms consisting of pulmonary fibrosis, kidney fibrosis, and cardiac fibrosis (Fig. 3). Pulmonary fibrosis is referred as a disease condition indicated through atypical accumulation of ECM resulting to damage, scarring and sclerosis of lung tissues [107]. It usually occurs in different forms such as idiopathic pulmonary fibrosis (IPF) etc. [108–110]. Till-date, the life expectancy associated with IPF after detection is short and as well as possess unknown pathogenesis [111]. The existing drugs utilized in the treatment of these aforementioned class of fibrosis lacks potentiality, especially in chronic stages. Therefore, further discovering of more potent drugs is required. It has been reported by few experimental studies that CGA promotes BLM-activated pulmonary fibrosis through inhibition of endoplasmic reticulum stress [96].

In kidney fibrosis, Arfian et al. found that CGA alleviates kidney ischemic/reperfusion injury through inhibiting inflammation, myofibroblast formation and tubular injury [97]. CGA also attenuated kidney fibrosis via regulating anti-fibrotic effects of hepatocyte growth factor (HGF) and bone morphogenetic protein-7 (BMP-7) [98]; suppressed the inflammatory response in kidney disease (ischemic reperfusion injury) through decreasing the production of pro-inflammatory cytokines [99]; as well as inhibits renal fibrosis and proteinuria via anti-oxidation and attenuating deposition of ECM [100].

On the other hand, regarding cardiac fibrosis, some studies proved that CGA protects cardiomyocytes from TNF-α activated injury through suppressing JNK and NF-kB actions [101]; inhibits acute myocardial infarction via diminishing oxidative stress and inflammatory damage [102], and attenuated hyperglycemia triggered cardiac fibrosis via activating the NO/cGMP/PKG mechanism [103].

In summary, CGA, inhibits the fibrosis associated with pulmonary fibrosis through down-regulation of endoplasmic reticulum stress;
| No | Conditions                        | Biological Sex | Application | Analytical Findings                                                                 |
|----|----------------------------------|----------------|-------------|-------------------------------------------------------------------------------------|
| 1  | Metabolic syndrome               | Male wistar mice | In-vivo     | Alleviates high-fat-diet, high carbohydrates triggered liver, cardiovascular and metabolic alterations. |
|    | -                                | Male tsuzuki obese diabetes rats (TSOD) | In-vivo     | Ameliorates the disrupted plasma short-chain fatty acids (SCFA) and gut microbiome. |
| 2  | Obesity                          | Male Sprague-dawley mouse | In-vivo     | Diminishes food intake, weight gain, circulating triglycerides and their accumulation in the liver (liver steatosis). |
| 3  | Hyperlipidemia                   | Male C57BL/6 J rats | In-vivo     | Stimulates body weight loss and altered mRNA expressions of lipolysis and lipogenesis associated genes in the adipose tissue. |
|    | -                                | Female ICR rats | In-vivo     | Decreases serum insulin level, abnormal islet hyperplasia, and adipose tissue activity. |
| 4  | NAFLD and atherosclerosis        | Male Sprague-dawley rats | In-vivo     | Potentiates heme oxygenase-1 expression (HO-1), and peroxisome proliferator activated receptor gamma, coactivator 1α (PGC-1α). |
| 5  | Diabetic nephropathy             | Male Sprague-dawley mice | In-vivo     | Down-regulates fats deposition in the liver, blood lipid levels, and peroxisome proliferator activated receptor gamma, coactivator 1α (PGC-1α). |
| 6  | Diabetes                         | Female Sprague-dawley rats | In-vivo     | Represses triglycerides, acetyl-CoA carboxylase (ACC), plasma free fatty acids (FFA) and increased carnitine palmitoyltransferase-1 (CPT-1) via activation of AMPK mechanism. |
| 7  | Hypertension                     | Male SHR and wistar-Kyoto rats | In-vivo     | Potentiates heme oxygenase-1 expression (HO-1), and peroxisome proliferator activated receptor gamma, coactivator 1α (PGC-1α). |

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suppresses the oxidative stress, inflammation and fibrosis associated with kidney fibrosis via inhibiting the production of pro-inflammatory cytokines and TLR-4/BMP-7/NF-kB/HGF mechanism; and impairs the oxidative stress and inflammation linked to cardiac fibrosis through diminishing ECM accumulation and JNK/NF-κB/PKG/NO/cGMP signaling pathways.

Potential utilization of CGA for the therapeutics of cancer

The application of CGA in cancer treatment (Table 3) has been enormously reported and demonstrated in cell lines, preclinical and clinical assays, owing to its outstanding and strong anti-cancerous effects [112–116]. As stated by the National cancer institute, cancer is referred as group of disease condition that involves atypical and excessive growth of cells, basically driven through a genetic process indated via genome instability and mutations observed at a cellular level [117, 118]. It is commonly classified or categorized as breast cancer, endometrial cancer, prostate cancer, pancreatic cancer, cervical cancer, brain cancer, colon or colorectal cancer, bladder cancer, gastric cancer, kidney cancer, stomach cancer, skin cancer, lung cancer, bone cancer (osteosarcoma) and blood cancer (leukemia) respectively [119]. The metastasizing signs and symptoms known to be associated with cancer includes lumps, unexplained weight loss, persistent cough or heavy breathing, abnormal bleeding, and skin changes. Interestingly, these fundamental manifestations frequently occurs at early and late stages of the disease, and triggered by some certain risk factors such as excessive alcohol intake, high body mass index (obesity), low vegetables and fruits (poor diet), lack of physical activity, biological carcinogens (parasites, bacteria or viruses), physical carcinogens (ionizing and ultraviolet radiation), and chemical carcinogens (aflatoxin, tobacco smoke, and arsenic) [120]. Moreover, cancer still poses a significant economic, social and clinical burden worldwide.

Chlorogenic acid for the therapeutics of lung cancer

It was revealed by few experimental studies that CGA suppresses the growth of adenocarcinomic human alveolar basal epithelial cells (A549 cells) via targeting the annexin A2 (in vivo and in vitro) [121], and modulates the gene expression of stem cell associated markers and apoptosis [122]. CGA also activates cellular DNA damage and formation of topoisomerase-I and II DNA complexes [123]. In addition, CGA regulates apoptosis in non-small cell lung carcinoma (NSCLC) via Notch1-signaling pathway [124], and, modulating histone deacetylase-6 [125].

Chlorogenic acid for the therapeutics of breast cancer

Some studies proved that the combination of CGA and lapatinib significantly represses metastasis via inhibiting macrophage M2 polarization in breast cancer [126]. CGA triggers apoptosis, obstructs metastasis, and enhanced anti-tumor immunity through the NF-kB signaling pathway [127]. An herbal medicine containing CGA and astragaloise as its active constituents proved to have remarkable anti-cancerous effects against breast cancer [128]. Also, the combination of CGA (aqueous extracts of Coffea arabica) and vitamin C elicits MCF-7 apoptosis or cell death [129]. Furthermore, CGA activates 4T1-breast cancer tumor’s apoptosis through regulating Bcl-2, caspase-3, Bax, and p53 mechanism [130, 131].

Chlorogenic acid for the therapeutics of colon cancer

Several assays demonstrated that CGA, an essential component of coffee phenolic phytochemicals altered the levels of ATF-2 modifying cyclin D1 and STAT5B expression [132], and inhibits metastasis via targeting MEK and TOPK mechanism in colon cancer cells [133]. CGA, and its microbial metabolites also exerts S-phase cell cycle arrest, anti-proliferative actions, and apoptosis in human colon cancer Caco-2 cells [134]. The combination of CGA and caffeic acid elicits positive inhibitory actions on cellular uptake and cell viability in human colon adenocarcinoma cells [135]. Additionally, CGA, the principal phenolic compound obtained from water extract of Hypericum androsaemum, hinders the proliferation in human colorectal cancer cells via acting on phosphoinositide 3-kinase (PI3K) or protein kinase B (Akt) and mitogen-activated protein kinase (MAP kinase) signaling pathways [136]. CGA plays a chemoprotective role against direct carcinogen in the colon of wistar mice [137], triggers reactive oxygen species (ROS) generation and decreased the viability of human colon cancer cells [138]. Moreover, CGA complex exerts significant anti-cancer actions in cultured HCT-116 cells [139].

Chlorogenic acid for the therapeutics of liver cancer

It was reported that the addition of CGA potentiates regorafenib actions in human hepatocellular carcinoma (HCC) cells [140]. CGA also promotes 5-fluorouracil effect in HCC cells via attenuating the extra-cellular signal regulated kinases (ERKs) [141], exerts positive inhibitory effects in HCC (in vitro and in vivo) cells [142], and reduced malignant attributes of HCC cells via suppressing DNMT1 expression [143]. Additionally, CGA enhanced the oxidative stress-mediated apoptosis via

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**Table 1 (continued)**

| No | Conditions          | Details of Assay               | Biological Sex | Application | Analytical Findings                                                                 | Refs |
|----|---------------------|--------------------------------|----------------|-------------|-------------------------------------------------------------------------------------|------|
| 8  | Neuropathic pain    | Chronic constrictive nerve     | Male sprague-dawley mice | In-vivo     | Study 1: Prevents the occurrence of mechanical hyperalgesia.                         | [88] |
|    |                     | injury (CCI) induced model      |                |             | Study 2: Alleviates cold and mechanical hyperalgesia partly via triggering GABAergic transmission in the spinal cord. | [89] |

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Fig. 1. Chemical structure of CGA.
activating the nuclear factor erythroid 2-related factor 2 (Nrf2) in hepatocytes [144].

Chlorogenic acid for the therapeutics of blood cancer

Another studies indicated that CGA triggers apoptotic cell death in U937 leukemia cells via mitochondria and caspase dependent mechanism [145], and in human acute promyelocytic leukemia cells (HL-60 cells) through suppressing the proliferation [146]. CGA also activated the apoptosis of Bcr-Abl (+) chronic myeloid leukemia cell and clinical leukemic samples via suppressing the Bcr-Abl phosphorylation [147], decreasing Bcr-Abl tyrosine kinase and inducing p38 mitogen triggered protein kinase-dependent apoptosis [148]. In addition, the metamorphosed root extract of *Rhaponticum carthamoides* and *Leonurus sibiricus* L., highly rich in caffeoylquinic acid derivatives (CGA), exerts strong anti-cancer effects in human leukemia and lung adenocarcinoma cells [149, 150].

Chlorogenic acid for the therapeutics of brain cancer

In recent years, CGA, obtained from normal and transformed roots of herbal plant known as *Rhaponticum carthamoides* and *Leonurus sibiricus* L., suppresses the proliferation of human glioma cell (HGC) via altering the Bax/Bcl-2-p53 expression and apoptotic activation [151, 152],

Table 2
Molecular actions of chlorogenic acid on various forms of fibrosis.

| No | Types of Fibrosis | Disease | Details of Assay | Biological sex | Application | Analytical Findings |
|----|------------------|---------|----------------|----------------|-------------|---------------------|
| 1  | Liver fibrosis   | CCl4 induced model | Male sprague-dawley mice and LX2 cells line | In-vitro and In-vivo | Significantly down-regulates the protein expression of α-SMA, TGFB-1, p-smad2/3, p-smad3, p-smad2, TIMP-1, and CTGF and mRNA expression of α-SMA, TGFB-1, TIMP-1, CTGF, and miR-21 levels. Promotes protein and mRNA levels of MMP-9, and Smad-7; Decreases the expression of COL-I and α-SMA in liver tissue, degree of liver fibrosis and TGFB-1/β in serum. | [90] |
|    |                  | Schistosoma japonicum cercaria model | Male BALB/c mice and LX2 cell line | In-vitro and In-vivo | Diminishes the mRNA expression of CTGF and miR-21, and protein expressions of α-SMA, TGFB-1, p-smad2/3, p-smad3, p-smad2, and CTGF. Increases mRNA and protein expression of Smad-7. Modulates the in-vivo interaction of IL-13/miR-21/Smad7 signaling pathway | [91] |
| 1  | Liver fibrosis   | CCI4 induced model | Male Sprague-dawley rats | In-vivo | Attenuates the expression of COL-I, TIMP-1, α-SMA, COL-III, degree of liver fibrosis, hydroxyproline content; CYP2E1, MDA, hepatic stellate cells proliferation, p38 and ERK1/2 phosphorylation, ROS production, levels of pro-fibrotic genes and NOX subunits (p47phox and gp91phox). Potentiates the expression of SOD, CAT, and GSH in liver tissues, Nrf2 and Nrf2 modulated anti-oxidative genes (NQO1, GCLC and HO-1). | [92] |
| 1  | Liver fibrosis   | CCI4 induced model | Male sprague-dawley mice | In-vivo | Inhibits the mRNA expressions of COL-I, COL-III, VEGF, bcl-2, Bax, and TGFB-1, protein level of α-SMA, GRP78 and GRP94, and degree of liver fibrosis. | [93] |
| 1  | Liver fibrosis   | CCI4 induced and inflammation model | Male sprague-dawley mice | In-vivo | Suppresses the levels of α-SMA, COL-I, serum transaminase, degree of fibrosis, IFN-α, TRAF4, COX-2, MyD88, NF-kB activation, serum and mRNA expression of TNF-α, IL-1β and IL-6. Elevates the expression of bone morphogenetic protein and activin membrane-bound inhibitor. | [94] |
| 2  | Pulmonary fibrosis | Bleomycin induced model | Male BALB/C rats | In-vivo | Reduces expression levels of GRP78, α-SMA, CHOP, and COL-I in dose-dependent manner, caspase-3, caspase-9, caspase-12, PERK phosphorylation, and cleaved ATF-6. Promotes uncleaved PARP expression, and proliferation of RLE-6TN triggered via TGFB-1. | [96] |
| 3  | Kidney fibrosis  | Male Swiss background rats | In-vivo | Reduces myofibroblast and macrophage number, mRNA level of NF-kB, TNF-α, TRL-4, and MCP-1. | [97] |
| 3  | Kidney fibrosis  | Adult male Swiss webster rats | In-vivo | Decreases α-SMA. Improves mRNA expression of bone morphogenetic protein-7, and hepatocytes growth factor. | [98] |
| 3  | Kidney fibrosis  | Male Swiss rats | In-vivo | Hinders the inflammatory response via decreasing TRL4, COX-2, TNFα expressions, and NF-kB action. Suppresses levels of creatinine, and BUN (blood urea nitrogen) to effect kidney optimal activities. | [99] |
| 3  | Kidney fibrosis  | Adult Wistar mice | In-vivo | Diminishes the creatinine, BUN, proteinurea, oxidative stress, COL-IV, fibronectin, p-smad2 and TGFB-1 expressions in kidney tissues. | [100] |
| 4  | Cardiac fibrosis | Male C57BL/6 N mice | In-vivo | Reverses TNF-α triggered cellular injuries. Ameliorates cell viability, mitochondrial membrane potential, ERK1/2, and attenuates cardiomyocytes apoptosis and c-Jun N-terminal kinase. Hampers NF-kB signal via inhibiting NF-kB/p65 phosphorylation. | [101] |
| 4  | Cardiac fibrosis | Male Sprague-dawley mice | In-vivo | Alleviates weight gain, plasma level of myocardial markers, myocardial injury, fibrosis, and pro-inflammatory factor expressions of IL-6, TNF-α, INF-γ, and IL-1β. Upregulates actions of IL-10 and IL-4 anti-inflammatory cytokines, including CAT and SOD enzymatic antioxidants. | [102] |
| 4  | Cardiac fibrosis | Male C57BL/6 N mouse | In-vivo | Activates the cyclic GMP/protein kinase G pathway to obstruct hyperglycemia triggered nuclear translocation of p-smad2/3. Attenuates pro-fibrotic gene expression in cardiac fibroblasts. Potentiates cGMP level and induced PKG in cardiac fibroblasts via increasing NO production and endothelial nitric oxide synthase (eNOS). | [103] |
activates apoptosis in HGC lines of different grades via reactive oxygen species-mediated mitochondrial mechanism and caspase induction [153, 154], and impaired HGC viability through activation of double strand DNA damage, H2AX phosphorylation, and Poly [ADP-ribose] polymerase 1 (PARP-1) cleavage [155]. Moreover, CGA with Arabidopsis thaliana production of anthocyanin pigment 1 (AtPAP1) transcriptional factor triggered apoptosis via DNA damage and inhibition of selected epigenetic factors in HGC [156].

Chlorogenic acid for the therapeutics of other cancer

Other form of cancers in which CGA was found to have potent effects includes blood cancer, skin cancer, kidney cancer and pancreatic cancer. In bone cancer, CGA reportedly induced extracellular-signal-regulated kinase1/2, and inhibits the growth of osteosarcoma cells [157]. However, for skin cancer, the fruit extracts of an herbal plant known as Sorbus commixta, constituting of CGA as its major phytochemical
| No | Types of Cancer | Details of Assay | Application | Analytical Findings | Ref. |
|----|----------------|-----------------|-------------|--------------------|------|
| 1 | Lung cancer | Male BALB/c nude mice and human lung cancer A549 cell | In-vivo and in-vitro | Effectively diminishes the binding of annexin A2 to p50 subunits, and expression of downstream anti-apoptotic genes cIAP1 and cIAP2 via NF-κB signaling pathway. | [121] |
| 2 | Breast cancer | Mouse 4T1 breast cancer cell | In-vitro | Attenuates cell proliferation, expression levels of BCL2, and stem cell-related markers (SOX2, POU5F1, and NANOG); triggered JNK and p38 MAPK gene expression; and elevated expressions of CASP3, BAX, and annexin V. | [122] |
| 3 | Colon cancer | Human cancer A549 cell | In-vitro | Induces DNA damage, high level of topoisomerase-I and topoisomerase-II DNA complexes in cells. | [123] |
| 4 | Liver cancer | HepG2 human hepatocarcinoma cell | In-vitro | Potentiates specific changes in the cell cycle, rate of apoptosis and repressed HT-29 cell viability. | [135] |
| 5 | Blood cancer | Human U937 leukemia cell | In-vitro | Potentiates death receptor DR5; triggered deposition of intracellular reactive oxygen species (ROS). | [141] |
| 6 | Brain cancer | Human glioma cell | In-vitro | Reduces cell proliferation and triggered apoptosis in a dose dependent manner. | [151] |

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ingredient indicated certain anti-melanoma effects [158]. On the other hand, CGA also suppresses proliferation and triggers apoptosis in human kidney cancer cells (A498 cells) through inactivation of PI3K/Akt/mTOR mechanism [159]. Finally, the combination of CGA, polyphenols and epigallocatechin gallate portrays synergistic anti-cancerous effects against human pancreatic cancer cells (PANC-1 cell) [160].

Inhibition of cancer-related epithelial mesenchymal transition by CGA

The preservation of homeostasis and architecture in a healthy tissue is usually accompanied or characterized through epithelial integrity and inhibition of plasticity. Epithelial-mesenchymal transition (EMT), an essential cellular mechanism in cancer progression, is a process whereby cells go through functional and phenotypical changes resulting to a mesenchymal-like function and state. EMT, as a physiological process is generally involved in the regeneration of tissue, wound healing and embryogenesis. Numerous factors and conditions such as TGF-β, oxidative stress, tissue injury and inflammation, hippo pathway stimulation, hypoxia and HIFα release as well as improved biochemical stress have been reported to trigger EMT [161–163]. The significant EMT-associated transcription factors, ZEB, TWIST, bHLH, and SNAIL, inhibits the level of epithelial proteins involving E-cadherin, and activate protein expression related with mesenchymal phenotypes like N-cadherin, Vimentin, MMP9, Fibronectin, and MMP2 [164, 165].

Table 3 (continued)

| No | Types of Cancer | Details of Assay | Application | Analytical Findings | Ref. |
|----|-----------------|-----------------|-------------|---------------------|-----|
| 7  | Bone cancer     | U87MG and patients-derived IV grade glioma cells | In-vitro   | Alleviates UHRF1 and DNMT1. Activates double strand DNA damage via promoting the number of phosphorylated H2A.X and cleaved PARP1. | [155, 156] |
| 8  | Skin cancer     | Human melanoma (SK-MEL-2) cell | In-vitro   | Mediates apoptosis via suppression of MEK/ERK mechanism and enhanced caspase-3 activity. | [158] |
| 9  | Kidney cancer   | A498 human kidney cancer cell | In-vitro   | Activates proliferation via induction of caspase protein and up-regulating pro-apoptotic protein Bax ratio to anti-apoptotic protein Bcl-2. | [159] |
| 10 | Pancreatic cancer | Human pancreatic cancer PANC-1 cell | In-vitro   | Hampers cellular proliferation, causes cell cycle arrest, triggers apoptosis and loss in the mitochondrial membrane potential. | [160] |

over a decade, experimental studies have shown that effectual suppression of EMT plays a crucial part in treating cancer metastasis. Fig. 4 demonstrates CGA effects in the inhibition of cancer-related EMT. It has been reported that CGA, an essential component of Annurca apple polyphenol extract, potentiates EMT and suppressed migration in MDA-MB-231 and MDA-MB-468 triple-negative breast cancer cells (TNBC), and inhibits metalloproteinase-2 (MMP-2) and metalloproteinase-9 (MMP-9) via JNK/ROS mechanism. In addition, CGA also downregulates the expressions of phospho-Smad-2/3 (p-SMAD-2/3) and Smad-2/3, upregulates N-cadherin/E-cadherin protein ratio, triggered the switch from N-cadherin to E-cadherin expression and significantly diminished vimentin levels [166]. Furthermore, an in-vitro studies found that CGA derivative (isochlorogenic acid C) reverses EMT through inhibition of Epithelial growth factor receptor (EGFR)/Phospholipase Cγ (PLCγ)/Extra cellular regulated protein kinase 1 or 2 (ERK1/2)/Slug signaling pathway in MDA-MB-231 cells [167]. These few analysis suggested that CGA possess a down-regulatory action against EMT and could be applied in treating cancer. The EMT reversal might have the significance of improving the regeneration of dispersed cancer cells [168]. Therefore, for better understanding regarding cell plasticity, further in-vivo and in-vitro studies should be carried-out to analyze the combined outcomes of CGA for anti-EMT remedy.
Conclusion and future perspective

Consolidally, CGA could serve as prospective drug candidate utilized in fibrosis and cancer treatment. Reports have shown that CGA portrays anti-fibrotic and anticancer effects through suppression of inflammation, cellular senescence, epithelial mesenchymal transition (EMT), hippo mechanism activation, ECM modification, genetic alterations, TGF-β overproduction, fibroblast proliferation and differentiation, elevating invasiveness and stiffness respectively. As a phenolic compound sourced naturally, it is known to possess minimal toxicity level as well as multiple pharmacological attributes such as anti-metastatic, anti-oxidative, nephroprotective, anti-inflammatory, anti-diabetic, anti-hypertensive, hepatoprotective, anti-bacterial, neuroprotective, anti-proliferative, central nervous system stimulator, anti-obesity, cardioprotective, anti- pyretic, anti-viral, and anti-angiogenic respectively. Presently, although CGA has been recognized and approved for phase-I (NCT02729349, Apr. 2016) and phase-II (NCT035758014, Nov. 2018) clinical trials by the China Food and Drug Administration (CFDA) as a possible drug for cancer in glioma patients. Yet, its molecular mechanism still remains unclear. Numerous experimental studies carried-out by researchers regarding CGA, most especially through the use of cell or animal model have demonstrated its great significance and positive therapeutical effects against fibrosis and cancer. Moreover, with regards to finding more potent drugs and ascertaining a clinical breakthrough in fibrosis and cancer therapeutics universally, more studies using human model needs to be conducted in the future. In addition, the metabolism, excretion, utilization and bioavailability of CGA also requires further experimentation.

Declaration of Competing Interest

The authors declare no conflict of interests.

Consent

This literature review does not contain studies with human participan ts or animals performed by any of the authors.

Credit authorship contribution statement

Ebuka Oliwaemeka Nwafor conceived the manuscript and figures; Ebuka Oliwaemeka Nwafor and Peng Lu wrote the manuscript; Ebuka Oliwaemeka Nwafor and Peng Lu wrote the manuscript; Zhidong Liu supervised and edited the manuscript.

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