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Protective effect of natural products and hormones in colon cancer using metabolome: A physiological overview

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ABSTRACT

Globally, the third cause of males cancer and the fourth cause of females cancer is colon cancer (CC). In Egypt, high CC percentage occurs in children and in individuals below 40 years of age. The complete loss of biological enzyme function is the main cause of CC and consequently CC increased in smoking and pollution exposure. The aim of this review is to focus on the application of metabolome as a physiological tool that can play an important role in preventing CC incidence by natural products and hormones. The dietary factors, intestinal micro-flora and endogenously produced metabolites are the main three causes that produce free radicals in the colon. A correlation occurs between the enzyme activity and CC polymorphisms or property. Nowadays metabolome is applied with the progress of different analytical methods, data bases and tools for cancer predication and stimulation especially in CC cases. Metabolism is defined as intracellular chemical reactions that produce chemical substances and energies sustaining life. Metabolic pathway networks are also composed of links that are defined as transformation of chemical structures between two metabolites and an enzyme reaction. The most important advantage of metabolome is its ability to analyze metabolites from any source, regardless of origin, where the application of liquid chromatography combined with mass spectra in metabolome analysis to a series of cancer cell lines that were progressively more tumorigenic due to the induction of 1,2,3 or 4 oncogenes to cell lines could be a metabolome example application. In conclusion, natural products and hormones are very important in preventing CC in humans and animal models where both natural products and hormones play a significant and important effect in regulating physiological process especially in CC cases. In this situation, metabolome must increase in its application in the future for the diagnosis of CC cases.

1. Introduction

Globally, the third cause of male cancer and the fourth cause of female cancer is colon cancer (CC). The incidence and percentage of CC in the world varies from one place to another. It is the principle and main cause of cancer mortality in United States, Europe, Asia and Africa [1,2]. The incidence of CC jumps from one into seven in North Africa (Morocco, Algeria, Tunisia, Libya and Egypt) during the last few years where CC incidence occurred in. 9.7% of the total regional population. The CC incidence data is good and available to draw the CC curve in the last decade. The CC incidence in North Africa countries varied from 1/4 or 1/2 or 1/3 that occurred in European countries. In Sètif, Algeria, the incidence of CC in men = 94.0 per 100 000 populations while the incidence of CC in men = 162.9 per 100 000 populations in Garbiah, Egypt [3]. There are many clinical and experimental studies established a correlation between CC incidences and some food type's intake. Increased age and body mass index are proportional to CC incidence and percentage. Dietary supplementation of proteins, fiber, fruits, grains, meats, coffee, alcohol, aspirin and vegetables were not associated with CC mortality [4]. The CC incidence is reduced by quercetin supplementation in an experimental model. This inhibition of CC by quercetin is

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related to regulatory action of quercetin on Wnt signaling and induction of apoptosis [5]. The genetic deviations are found to have effect on CC progress where The *TLR-9* gene has an anticancer role in CC progress, on the other hand, the SNPs in *TLR-9* genes are the biomarkers determined before the treatment of CC females occurred [6]. The advanced CC is treated in the last few years by targeting deregulated proteostasis new technique through the induction of destructive stress that overcomes multiple resistance mechanisms associated with translation inhibition [7]. Another treatment used in CC is 5-fluorouracil (5-FU). The 5-FU stimulates Sestrin (SESN) 2 role in CC cells where 5-FU initiates SESN2 protein expression in both HCT116 and HT29 cells. In the same time, 5-FU enhances transcriptions of SESN1 and SESN2 but inhibits transcription of SESN3. The 5-FU increases the level of SESN2 protein expression through *p53*-dependent pathway, which leads to the decrease of cancer cells [8]. Compared with neutral pH cells, there is a rise release for disulfiram nanoparticles in CC cells. Also, compared with normal cells, disulfiram uptake increases in CC cells by using Zeta potential of coated nanoparticles. An increase discharge of nanoparticles in CC cells is related to increase of apoptosis rate and removing cancer stem cells in CC cells. Consequently, disulfiram is the most effective and selective for eradicating CC stem cells without insulting normal stem cells [9].

This article aims to focus on the application of metabolome as a physiological tool that plays an important role in CC prevention by using certain natural products and hormones.

2. CC in Egypt

The Gharbiah governorate in Egypt recorded high gastrointestinal lymphoma (GIL) incidence in all other Governorate in Egypt which equal to 6.2% of all GIT cancers. The median age was 47 years with slight male predominance. The common primary site was the stomach followed by the colon/rectum then the small intestine (67.5%, 25.0% and 7.5% respectively). The common histological subtypes were the diffuse large B-cell (41.5%) followed by marginal zone B-cell (39%). The common symptoms were abdominal pains followed by vomiting. Only 18% of GILs were surgically resected. Most patients (77%) received chemotherapy with a 60% complete response rate. So, GILs in Gharbiah, Egypt are characterized by predominance of male gender, gastric site and marginal zone histology [10]. In another study, from the 142 cases with CC, 15.5% and 33.1% were affected before 40 and 50 years of age respectively. Emergency rooms were main referral sites for CC cases (31.0%). Right colon was affected in 16.9% while left colonic lesions accounted for 62.7%. Intestinal obstruction was the main presentations (41.5%), and 26.1% presented with symptoms indicating distant metastatic lesions. Adenocarcinoma was the predominant pathological lesions (86.6%). Metastatic CC was diagnosed in 62.7%. Duke's staging showed that 22.5% and 40.1% of lesions were classified into C and D categories respectively [11]. A study was conducted to reveal the pattern of different gastrointestinal malignant neoplasms in Alexandria in the last decade (1987–1996). All registered cases of GIT cancers in Alexandria. Main University Hospital in the last decade was included in the study. The total number of cancer cases in Main University Hospital in Alexandria in the last decade was 2 184, 58.6% were males and 41.4% were females. The mean age of registered males cases was significantly older than females (t = 2.43). The highest percentage (47.2%) of cases were in the age group (40– <60 years). Of the latter category cancer pharynx came first in both sexes (49.9%) with the youngest mean age [(45.65 ± 15.79) years], followed by cancer tongue (24.9%) with the oldest mean age [(58.56 ± 12.40) years]. Among cases of malignant neoplasms of digestive organs, CC came first in both sexes (26.9%) with the youngest mean age [(44.11 ± 14.08) years]. Cancer gall bladder came last (1.2%) with the oldest mean age [(55.80 ± 10.20) years]. Over the last decade, trend of malignant neoplasms of colon, rectum, liver and pancreas were increasing while the reverse was observed for cancer esophagus and stomach [12]. Over the 9-year period, 1 364 CC cases were included. The disease incidence under age 40 years was relatively high while the incidence in the age groups 40 and over was very low in the age groups 40–59 years, 60–69 years and >70 years respectively. The vast majority of tumors (97.2%) had no polyps and 37.2% of the patients presented with primary lesions in the rectum. CC was more common in patients from urban (55%) than rural (45%) areas of Egypt. The colon and rectal cancer incidence varies according to regional differences in 8 areas of the study province and these reveals different etiologic forms in this population. The recorded data of Egypt shows an increase of CC compared with the United States in subjects under age of 40 years. The results also shows significantly lower incidence of colorectal cancer in subjects over age 40 years compared to the same age group in the United States [13]. In Egypt, CC incidence age shows high percentage in children and adults below 40 years of age. The official records show 1 608 CC patients receiving treatment in 4 different cancer hospitals in Egypt for 3–10 years [1]. High intake of fat and phosphate food has been linked to colonic hyperproliferation and CC development [14]. The CC has unique characteristics in Egypt that differ from that reported in other countries of the western society. It was estimated that 35.6% of the Egyptian CC cases are below 40 years of age and patients usually present with advanced stage, high grade tumors that carry more mutations [15]. The early and continuous exposure to various environmental pollution, the different and uncontrolled mutational onset are correlated with high percentage of CC in children and the increase of CC percentage in Egypt need further studies [16].

3. Physiological concepts of CC

The microRNAs are involved in CC incidence and progress through stimulation of immune suppression and starts of drug resistance. The *miR-146a* was expressed in HT-29 cells of CC. The expression of *miR-146a* increases transforming growth factor-β, expression of interleukin-10 expressions and enhances regulatory T cells in peripheral blood mononuclear cells [17]. The cell growth suppression was observed by both colony formation experiment and cell viability test as a result of *miR-133a* overexpression in CC cell lines. In the same time, CC tumor growth in nude mice was inhibited due to *miR-133a* overexpression. Furthermore, cellular migration and invasiveness were reduced by *miR-133a* where *miR-133a* gene initiates an oncogene eukaryotic translation factor 4A1. The expression of oncogene eukaryotic translation factor 4A1 gene inversely related with that of *miR-133a*. Consequently, *miR-133a* plays a key role in CC by inhibiting cell migration,

invasion and proliferation through stimulates factor 4A1 (which acts as a tumor suppressor) [18]. In another study, relapse and metastasis are always found in CC and related to stem cell features. Compared to non-side population cells, SP CC cells were more tumorigenic *in vivo*, exhibited more invasive features and a greater ability to form colonies. Additionally, more cells were in G_0/G_1 phase and more highly expressed the multidrug resistance protein BCRP/ABCG2 [19]. On the other hand, M3 muscarinic receptor stimulates CC cell invasion, migration and proliferation *in vitro*. The expression of *CHRM3*, the gene encoding M3 muscarinic receptor, is recorded in primary CC expression. Compared to normal colon, *CHRM3* expression was increased up to 128-fold in 10 of 18 consecutive surgical cancer specimens (56%) and associated with metastatic migration. In 25 of 29 CC tissues (86%) showed cytoplasmic and plasma membrane expression of M3 muscarinic receptor compared to normal colon [20]. Furthermore, the complete loss of enzyme functions in the case of smoking lead to CC incidence. Numerous carcinogenic materials were included in tobacco such as aromatic amines, polycyclic aromatic hydrocarbons, heterocyclic amines and *N*-nitrosamines. There are many different human and animal metabolic detoxification and activation were observed after exposure to smoking carcinogenic materials. There are numerous metabolic pathways that are affected and changed by smoking carcinogenic materials such as cytochrome P-450, glutathione-S-transferases and NAD(P) H:quinone oxidoreductase 1 pathways [21]. On the other side, Bundscherer *et al*. investigated the effect of lidocaine on CC cell lines (HT-29 and SW480) *in vitro* [22]. A total of 1 000 μm lidocaine was capable to induce cell-cycle arrest in both HT-29 and SW480 cell lines, while cell proliferation does not show any inhibition. Moreover, there are two functional polymorphisms occurs in *CYP1A1* gene; one is 3698T > C substitution (*CYP1A1*2A*, rs 4646903) creating an *Msp*I restriction site in the 3′-flanking region, and the second is 2454A > G substitution (*CYP1A1*2C*, rs 1048943) resulting in an amino acid change in exon 7 (Ile462Val) [23]. In another clinical study, the CC life is lower in cases had greater expression of CC-associated transcript 2 (CCAT2) compared with CC cases had lower expression of CCAT2. The lower expression of CCAT2 leads to inhibition of CC cell propagation and stimulation of clear cell renal cell carcinoma (ccRCC) cells *in vitro* was reported in the same time. Consequently, CCAT2 in CC cases had a significant and important role in ccRCC development and progress. The CCAT2 was a biomarker for calculating and expecting the survival life of ccRCC cases and development of new treatment for ccRCC mediation [24]. In HT29 CC cells, the tumor volume was double that volume in HT29 CC stem cells. The *Portulaca oleracea* extract when administrated at (0.07–2.25) μg/mL repressed the expanding tumor volume of HT29 CC cells and HT29 CC stem cells. Consequently, *Portulaca oleracea* extract constrains CC stem cells progress in a dose dependent mode. Moreover, the extract decreases the *Notch1* and *β-catenin* genes expression in CC cells [25]. In another study, lower variation, increase T stage and clinical phase are associated with increase expression of CCAT2. These observations lead to CCAT2 can be used as an early and significant biomarker in oral squamous cell carcinoma. The CCAT2 could be stimulated again to malignant cases of oral squamous cell carcinoma cells through inhibiting β-catenin and increasing expression of glycogen synthase kinase 3 beta [26]. The glutathione-*S*-transferases (GSTs) antioxidants enzymes are a superfamily of detoxification enzymes that stimulates the inactivation of chemical carcinogens and environmental toxicants. GSTs consist of several classes of genes polymorphisms such as *GSTM1* and *GSTT1* related to tobacco-related CC. There is a complete loss of enzyme function in null genotypes and thus increased risk of tobacco-related CC [21].

4. Natural products and hormones

4.1. Natural products

4.1.1. Alpha lipoic acid (ALA)

ALA has the ability to stop cancer cells capability and progress in colon, breast and thyroid tissues. Moreover, ALA and its reduced form [dihydrolipoic acid (DHLA)] inhibit protein tyrosine phosphatases (PTP1B and SHP2) activities. ALA and DHLA have reducing effects on breast cancer cells capability and propagation [27]. The effect of ALA was minimal inhibition of cell proliferation induced by cilostazol *in vitro* study [28]. Considerable evidence suggests that the risk of CC is increased by the mutagenic actions of free radicals, which are produced during oxidation reactions. Dietary factors, the intestinal flora (bacteria) and endogenously produced metabolites contribute to the production of free radicals in the colon. The free oxidative radicals that are created in oxidative stress cases are diminished after dietary antioxidants administration. The mutagens such as malondialdehyde and lipid hydroperoxides are produced in vitamin E deficiency cases following polyunsaturated fats intake where these fats oxidized in human colon to produce these mutagens. Furthermore, there are a huge stream of reactive oxygen species (ROS) such as superoxide radicals (O^{2-}) produced from bacteria in feces. These ROS are generated in the intestinal lumen and the inflammatory cells are very close to colon that produce ROS. In addition, in recent *in vitro* study, the transcription and expression of nuclear factor κB (NFκB), the products of transcription and expression of genes that are under its control were included in ALA in the CC protection. This obtained result was supported by the anti-proliferative and/or cytotoxic effect of ALA on human CC cells (Caco-2) and human cervical carcinoma cells (HeLa) cells at ALA high concentrations. Consequently, ALA is a key trigger in the chemoprevention of CC and cervix carcinoma [29]. ALA stimulates and increases p53 protein stability and its apoptosis-enhancing effect where the pro-apoptotic effect of ALA is correlated with its p53-stabilizing activity. In the same time, ALA exerts a reducing role on the nuclear translocation of NFκB controlled by tumor necrosis factor-α. Consequently, ALA blocks NF-κB signaling pathway to stop ribosomal protein RPS6KA4-mediated p53 inhibition, which inhibits and stops CC growth and expanding [30]. ALA has the capability to inhibit initiation and expanding of many different kind of cancers where ALA has an important and significant role *in vitro* and *in vivo* studies as a protective agent [31]. ALA can stop tumor cell proliferation and clone tumor formation and this effect was proportional to time factor. So, ALA alone or combined with paclitaxel can stop NFκB overexpression and inhibit cancer cell expanding in breast tissues [32]. The cell progress is reduced by ALA administration which depends on ALA dose in human and mouse CC cell lines. Nearly (0.5–1.0) mM of ALA significantly decreases cell cancer moving compared with control. Similarly, ALA down-regulates invasion, adhesion and

colony formation. Also, ALA activates p53 and AMPK signaling pathways in human and mouse CC cells [33]. ALA protects against oxidative stress through promoting glutathione and glutathione-*S*-transferase levels in hypothalamus and sperm. In addition, ALA stops the decrease in dehydroepiandrosterone sulfate, testosterone and 3b-hydroxysteroid dehydrogenase, prevents the elevations in sex-hormone-binding globulin levels and shows normal sperm quality. The germ cell expanding shrinks, while DNA breakdown is decreased by ALA. Also, ALA has the capability to keep and maintain the membrane protein structure in sperms. So, ALA modulates oxidative stress and protects testosterone synthesis pathway through hypothalamus, testis pathway and sperm quality [34]. Antioxidant activity is observed for both oxidized and reduced (DHLA) forms of ALA [35]. Other antioxidants are generated from ALA/DHLA redox couple. The purified and microsomal P450 reductase enzyme is decreased as a result of ALA administration through alteration of the SH-groups via a thiol-disulfide exchange reaction [36]. DHLA occurs in both intra-cellular and extra-cellular after treatment with ALA leading to increase of cell antioxidant defense and function [37]. ALA has a therapeutic effect for several diseases such as hepatic disorder and diabetic polyneuropathy. Moreover, the effect of ALA or DHLA on cancer chemoprevention occurs. DHLA/ALA decreases lipopolysaccharide-induced two important mediators related with inflammation markers such as NO and prostaglandin 2 in skin cancer cells. The treatment with DHLA/ALA increases the expression of iNOS protein. So, DHLA/ALA has chemo-preventive agent in inflammation-associated tumor-genesis [38].

4.1.2. *Saccharomyces cerevisiae* (Sc)

Sc is a probiotic which is a living microorganism. This microorganism inside the human body maintains the bacterial balance in the digestive tract of mammals. Also, Sc includes in treatment of pathological conditions such as candidiasis, diarrhea, immune disorders, urinary infections, lactose intolerance, hyper-cholesterolemia and food allergy [39]. The cell growth is inhibited about 40%–50% for all cell lines in CC cases following pumpkin extract administration which is a good and excessive source of Sc. The CC cell expanding is reduced for firm growing CC cells together with reduction of prostate-, breast- and CC expanding cells communicate together to give rise to the use of pumpkin seeds for a treatment of benign prostate cancer [40]. Sc stimulates amygdalin (major component of the seeds of Rosaceae family plants such as apricots, peaches and cherry) to exert cytotoxic effect in CC cell lines with greater proliferative and metabolic activity. So anti-mutagenic or anti-recombinogenic effect is found through the activation of error-free and error-prone recombination events of both Sc and amygdalin [41]. In another *in vivo* study, a new synthetic derivatives of quercetin is 3,7-dihydroxy-2-[4-(2-chloro-1,4-naphthoquinone-3-yloxy)-3-hydroxyphenyl]-5-hydroxychromen-4-one (CHNQ). CHNQ had anti-cancer role in CC cells. CHNQ had induced oxidative stress and ROS. CHNQ-induced cytotoxicity, ROS formation and autophagy were also detected *in vivo* in *Saccharomyces cerevisiae* strain RDKY3615 [42].

Sc has benefit to health in many ways such as: (1) Stimulation of growth of intestinal microflora in mammals; (2) pH variation in ruminants (which gives rise to an increase in the rate of cellulite bacteria); (3) Enhancement of reproductive factors and fertility in cows, birds and fetal development; (4) Reduction in the number of pathogenic microorganisms in mono-gastric animals [43,44]. Sc activates the essential oils from spearmint and sweet basil demonstrated cytotoxicity against common foodborne bacteria [45]. In addition, Sc plays an important and key trigger role in KRAS mutation and expression in CC patients. Mutation and overexpression of KRAS-induced autophagy continues and accelerates by up-regulation of the MEK/ERK pathway in CC cases. The mutation of KRAS and autophagy contribute to CC cell survival in starvation [46]. Furthermore, a highly specific monobody E1 is useful as a human EphA2 specific candidate for *in vivo* diagnosis and therapy of many different kinds of tumors such as CC, breast and lung cancers types [47].

4.1.3. Citrus pectin (CP)

CP isolated from many sources and modified citrus pectin (MCP) has exhibited inhibition activity towards CC cell lines where CP isolated from sugar beet pulp affected the viability of CC cells. Alkali treatment increases the anti-cancer effect of sugar beet pectin through increased apoptosis [48]. The mutation and expression of galectin-3 in mice colon injected with azoxymethane induced CC in mice was decreased by the administration with modified citrus pectin alginate. Consequently, modified citrus pectin alginate increases the bioactivity and protective roles against both pre-CC lesions and CC adenocarcinoma through inhibiting galectin-3 and vascular endothelial growth factor in mice model of CC [49]. CP in combination with oxaliplatin stops HT29 cell expanding in dose-dependent and time-dependent manner. Consequently, CP enhances the capability of oxaliplatin to inhibit cell progress and induce apoptosis process which is correlated with acceleration of mitochondrial apoptosis pathway [50]. There are smaller numbers of liver metastases in high concentration of MCP compared with control group. Also, there are smaller numbers of the primary lesions in the spleen in moderate and high concentration of MCP compared with control group. Moreover, there are higher levels of serum galectin-3 expression and mutation in the MCP-treated groups compared with control group. There is no significant change in galectin-3 expression and mutation in the liver metastases in MCP-treated group compared with control group. Consequently, the expression and mutation levels of galectin-3 revealed significant increase in the liver metastasis in CC while MCP inhibits the liver metastasis [51]. The pectic acid inhibits cell growth in breast cancer. It also reduced breast cancer cell attachment after 24 h incubation where pectic acid induced caspase-dependent apoptosis [52]. Although pectin occurs in the majority of plant cell walls, it is most rich in citrus fruits such as lime, lemon, grapefruit and orange. There are fruit and vegetable by-products are rich nutrients and extra-nutritional compounds such as pectin. These vegetable by-products are important and useful to weight control, bowel health, decrease blood cholesterol levels and enhanced control of glucose and insulin responses [53].

The pectin in green cincau indonesian food inhibited Caco-2 cell viability and induced cell death in CC. Consequently, green cincau pectin had a protective role against CC [54]. The cell viability of CC adenocarcinoma cell was inhibited at higher dose of pectin varied from 0.1%, 0.2% and 0.25% w/v and increased the incubation period from 24 h to 48 h [55]. In another study, the authors combined pectin with chitosan to form chitosan-pectinate nanoparticle complex compound and applied this complex compound in treatment of CC [56]. In addition, the dietary pectin could modulate and stop the

mitochondrial metabolic pathways, and consequently restrain apoptosis and CC risk and incidence [57]. Furthermore, pectin could combine with lactoglobulin to form β-lactoglobulin-pectin nanoparticles which helps to transfer a newly synthesized, anticancer platinum complex to the colon to treat CC. These nanoparticles have capability to serve as new and efficient vehicles for oral drug delivery preparations [58]. The dietary pectin modulates noncoding microRNAs (miRNA) so it could be as protective agent in CC incidence where pectin up-regulates tumor suppressor miRNAs in intestinal mucosa and consequently inhibits CC incidence [59]. Moreover, CP elevates serum testosterone, dehydroepiandrosterone sulfate and lactate dehydrogenase. Also, CP increases testicular cholesterol, total protein, glucose-6-phosphate dehydrogenase, 3β-hydroxysteroid dehydrogenase and antioxidant enzymes. The CP inhibited testicular malondialdehyde level. Moreover, there is a decline in serum sex hormone binding globulin, follicle stimulating, luteinizing hormones and g-glutamyl transpeptidase in cadmium exposure animals while CP elevated the above mentioned parameters to approach the normal values [60]. The CP increases antioxidant enzymes levels while decreased lipid peroxidation, nitric oxide and protein carbonyls levels in the kidney tissues. On the other hand, CP has the capability to decrease kidney function while it increases kidney weight. CP has the ability to increase *p*53 gene expression while it decreases *bcl-2* gene expression in octylphenol toxicity kidney. So, CP has an antioxidant and anti-apoptotic activities [61].

4.2. Hormones

4.2.1. Estrogen

Estrogens prompt essential cellular responses in many target tissues such as reproductive organs, bone and cardiovascular system, and are incorporated in certain brain functions. Estrogens have also concerned in the growth and/or regulation of tumors related with breast, ovaries, endometrium, prostate and colon. The CC is minor in women than in men and this related to both oral contraceptive and estrogen replacement therapies are correlated with decreased risk of CC risk. There are variances in estrogen receptor-β expression and mutation, and these effects enable estrogen to modify the exposure to CC and consequently suggest a protective role of estrogen in CC incidence and progress [62]. The estrogen drug (ME-143) has the capability to inhibit most common CC type (DLD1) 10 times than genistein drug do at the concentration of 3.125 μm. The ME-143 has the ability to inhibit WNT/β-catenin pathway in CC tumor cells of various hereditary status [63]. The estrogen receptor-alpha was expressed only in the CC cells (DLD-1 and HCT-15) while estrogen receptor β expressed in CC cells (DLD1, HCT15, COLO205, LOVO, and SW480) [64]. Also, estradiol treatment inhibited inflammation in the middle CC and the distal CC mice compared to control. Injury scores were decreased in E_2-treated mice compared to control. E_2 had increased proliferation in the basal third of crypts in the distal colon and decreased apoptosis in the proximal colon [65]. Red and processed meat is associated with CC risk and incidence [66]. There are many studies had focus in the relation of obesity with increased risk of numerous cancer types such as colon, liver, kidney, breast, esophagus, gastric, endometrium, pancreatic, gall bladder and leukemia. There are numerous and different biological processes changes take place in the fixed relation of obesity and cancer such as inflammatory process, angiogenesis pathways, pro-inflammatory cytokines secretion and endocrine hormones roles *e.g*. estrogen and testosterone [67]. The treatment with genistein induces biological changes in enzymatic and non-enzymatic anti-oxidants pathways in CC animal models. In CC animal models, an oxidative stress was observed while genistein treatment stimulates expression and mutation of nuclear factor-erythroid 2 related factor 2 and hemoxygenase-1 [68]. Zearalenone is estrogenic mycotoxin that induces liver toxicity, immunity disturbances and hereditary toxicity. At minimum concentration of zearalenone cell propagation, colony development and cell movement were increased while at maximum effect of zearalenone was observed at a concentration 10 times lower as compared to aflatoxin B1 [69]. There is no correlation between dietary phytoestrogen consumption and CC incidence and progress in 206 Swedish CC women cases selected from 48 268 Swedish women aged 30–49 years between 1991 and 1992 [70]. The bisphenol A has the capability to mimic the biological endogenous hormones such as estrogen and testosterone. The minimum concentration (10 ng/mL or 1 μg/mL) of bisphenol A causes many different expression and mutation of 4 biomarker genes in HT29 human CC adenocarcinoma cell line [71].

4.2.2. Testosterone

The androgen hormone plays an important and significant role in the determination of sexual variation, growth of internal, external sex accessory organs and individual characteristics between sexes such as hair growth in certain body areas and muscle development. The androgens are formed and secreted into the blood stream in the form of testosterone. There are two new synthetic compounds of testosterone hormone [testosterone thiosemicarbazone, L and its nickel (II) complex 1]. These synthetic compounds had minimum toxicity was observed in human CC cells. In CC cells, these compounds were failed to inhibit the action topoisomerase I, which is the obvious and main goal in CC treatment [72]. Moreover, androgen receptors in membrane play a significant role in deterioration of CC through non-genomic androgen-dependent action sets. These receptors are separated from intracellular androgen receptors which promote CC incidence and risk. Also, testosterone–albumin conjugates connect to membrane androgen receptors and lead to apoptosis via caspase-3 activation [73]. The human cytochrome P450 2W1 enzyme is expressed in colon in two cases (fetus and tumor cases). The expression level is greater in colon metastases than in the parent tumors, and the enzyme is a good drug for treatment of CC. Consequently, normal adrenal tissue lacks P450 2W1 enzyme expression. Moreover, adrenocortical carcinomas generally do not express this enzyme [74].

The testosterone increased sexual activity in estrogens administered vaginally in hormonal treatment method [75]. The inhibition of testosterone through castration protects animals from CC adenoma incidence and progress. The dietary intake of testosterone reversed this effect. There is no androgen receptor was detected in the colon or adenomas, so the effect of testosterone is on the tumor line. Consequently, the role of testosterone on CC cells or adenomas provides more explanation on the difference between both sexes in CC cells or adenomas incidence [76]. In a recent prospective study includes 8 771 men and women observed precisely for more than 30 years, increased levels of testosterone were correlated with a 30%–80% increased risk of early death following

cancer, but the risk of incident cancer was unaffected in the same time [77].

5. Physiological concepts of natural products and hormones protection in CC

There is a relation between the enzymatic activity and CC incidence and progress [24]. The liver plays an essential role in the process of detoxication and elimination of toxic materials that enter the human body as lipid-soluble foreign compounds. The biotransformation is a biological process that transforms these lipid-soluble foreign compounds into polar water soluble metabolites that bound to the membranes of the smooth endoplasmic reticulum. The oxidating enzyme in biotransformation can be induced by certain toxins, drugs or carcinogenic materials. There is a chronic induction of enzymes by carcinogens and consequences of this process of adaptation, particularly in regard to the metabolism of calcium occurred. The protective effect of biotransformation and induction of enzymes against carcinogens, especially smoking, alcohol drinking and food poisoning are reviewed for CC. The first step leads to portal hypertension of the post-sinusoidal type, while the second step leads to pre-sinusoidal or intra-sinusoidal portal hypertension, after years of exposure, to hemangioendotheliosarcoma of the liver. Tumor is found in arsenic intoxication. Arsenic leads to non-cirrhotic portal hypertension. The gastrointestinal diseases and tumors as a result of environment factors are commonly accepted. The high incidence of gastric carcinoma in Japan and the varying occurrence of CC carcinoma in the modern and civilized world compared with the rural population of tropical regions are emphasized. The explanation for these facts is probably to be sought in differences of nutrition. In a recent study, *Salvia officinalis* administration has a protective role on CC. There is a decrease in monoclonal antibody Ki67 and in H_2O_2 produced, DNA damage decreased in colonocytes and lymphocytes in CC in *Salvia officinalis* administration [78]. Oral intake of lactobacilli has the ability to inhibit CC carcinoma and increased protective role of colon microflora in CC [79]. Dichloromethane extract of *Curcuma purpurascens* BI. rhizome (DECPR) upregulates *Bax* and downregulates *Bcl-2* genes through apoptosis process in CC animal model. Also, DECPR inhibits the oxidative stress in CC animal model after administration of DECPR. Consequently, DECPR inhibits aberrant foci formation in CC animal model and it had a protective role in CC incidence [80]. In another study, the dietary sulforaphane supplementation initiates and increases the NF-E2-related factor 2 and inhibits oxidative stress damage by decreasing H_2O_2 production. The oral intake of sulforaphane and selenium has the capability to increase thioredoxin reductase-1 expression which decreases and stops oxidative damage and consequently inhibits cell death observed in CC [81]. An inverse relationship was established between estrogen oral administration and CC incidence and progress. The preneoplastic lesions were decreased and inhibited by the effect of estradiol on estrogen receptor β in CC animal models. The protective role of estradiol was found through increased apoptosis process in non-malignant colonocytes which become carcinogenic in CC animal models. The increase of oral estradiol intake was accompanied with inhibit and repair of DNA double stranded breakdowns [82].

The LCS101 compound is extracted from herbal resource and shows decreasing effects on cancer cell growth and hematological toxicity in many types of cancers. The LCS101 compound has no effect on normal and healthy breast epithelial cells. The LCS101 compound increases and initiates cell death in cancer cells exposed to doxorubicin while it shows a protective effect on normal and healthy human epithelial cells. Consequently, the LCS101 compound has anti-carcinogenic effect in many types of cancer cells while it has protection to normal and healthy epithelial cells [83]. Furthermore, the basic fibroblast growth factor-stimulated and initiated fibroblasts play a key trigger role in the protection in cancer incidence, progress and migration. In the same time, the basic fibroblast growth factor also increases life-time of carcinogenic animal models. The serum immunoglobulins have the ability to stop the expanding of carcinogenic cells and fibroblasts *in vitro*. The serum immunoglobulins have the anti-carcinogenic effect *in vivo*. The anti-carcinogenic effect was retracted through decreasing CD4(+), CD8(+) T lymphocytes and NK cells [84]. In addition, daily oral intake of selenium and green tea plays an important role in cancer incidence and progress in CC animal models. The daily oral administration of both selenium and green tea caused a significant and obvious inhibition of CC compared with oral administration of selenium or green tea alone. The combination of selenium and green tea has a greater inhibition than selenium or green tea alone on cancer incidence, progress and size. The combination administration of selenium and green tea inhibited cyclin D1 expression, β-catenin nuclear translocation and CC cell proliferation. Consequently, combination of selenium and green tea is more effective in inhibition CC than either agent alone. The protective role is correlated with controlling genetic and epigenetic biomarkers involved in CC incidence and progress [85]. In other research, the combination of limonoids with curcumin inhibits CC cell lines by 96%. The combination of limonoids and curcumin increases caspase-3 activity and Bax/Bcl-2 ratio. Consequently, combination of curcumin and limonoids has a protective role in CC incidence and progress [86]. The coffee has an important and significant role in inhibiting CC incidence and progress through its constituents that reach the human colon such as coffee polyphenols and dietary fiber, including melanoidins. The coffee has a greater and significant effect on human colon. It causes human biological deregulation that induces CC. The colon microbiota and lumen inhibiting factors were involved in human biological deregulation. The coffee chlorogenic acids and dietary fiber including melanoidins, inhibit CC incidence while increasing colon moving and antioxidant status [87].

6. Metabolome as a physiological tool in diagnostic, protective and treatment in CC

Nowadays metabolome become apparent with the development of analytical methods, data bases and tools for predication and stimulation. Metabolism was defined as intracellular chemical reactions that produce chemical substances and energies sustaining life. Metabolic pathway networks are also composed of links that are defined as transformation of chemical structures between two metabolites and an enzyme reaction. Metabolites and chemical mechanisms are the same throughout biological species. Biomarkers have been defined as such a set of metabolites that are characteristics to an internal or an external perturbation; organic acids in urine are used as the biomarkers to detect some diseases in patients. The nuclear magnetic

resonance was used to evaluate the protective role of *Camellia nitidissima* Chi extracts in CC animals models. Their effect was done through stopping the colon inflammatory markers, attenuates serum biochemistry and converses the disturbed metabolic process to the normal case. Consequently, *Camellia nitidissima* Chi extracts had a greater effect to CC inhibition [88]. Metabolite profiles are much more informative for defining unidentified diseases and cancers. Also, metabolome can be used as a tool of drug development, where drug design is composed of two steps. The first step is lead finding, the second step is lead optimization. Lead is compound of a new chemical structure and has only a weak drug activity, often accompanied by toxic side effects. Lead has the ability to improve the drug action of a lead compound by (1) modifying the site of its biochemical action and target protein; (2) revealing the mode of protein–drug interactions; (3) predicting *in vitro* activity of drug candidates by analyzing the relationships between their chemical structures and drug activities. Detecting side effects or toxicity of drug used is also a purpose of animal and clinical tests. Metabolite profiling has a potential to detect such covert and unfavorable biological effects. Metabolic apply in medicine as a tool for diagnosis, follow-up and pathophysiological disorders analysis. The metabolic pathway of CC is abnormal and irreversible disorders in human metabolite profiles. In many clinical diagnosis measure enzyme activities in the patients' blood as ordinary way. The metabolome investigation is essential and necessary method to find sicknesses in CC patients where metabolite analysis should be added as a clinical tool of diagnosis. When metabolite profiles from CC patients with various cancer degrees are collected, we can use them as a template for diagnosis, if metabolite profile from CC patient were equal to one of the templates, we could isolate CC patients' disease. The metabolome can be used to recognize human or animal host metabolism that affect CC progress and expanding, as well as response of CC cells to specific treatment [89].

Combined analysis identifies the enzyme reactions and metabolites that are disordered, and is indispensable for analysis of physiological and environmental perturbations on the metabolite profile of a patient. The gas or liquid chromatography or capillary electrophoresis associated with mass spectrometry is the common metabolome instruments used. These instruments detect metabolite urine, serum, blood or tissue of patients and animal models which have genetic disturbances on their metabolic processes through expressions or RNA breakdowns. The metabolome profiles involved in this process include amino acids, organic acids, choline esters and glucose. The computation methods of intracellular biological metabolic changes inside the cell through combination of time factor with quantitative metabolome calculation were used. Development of standard protocols for the extraction and analysis of metabolite from human and animal tissues are now in progress for acquisition of reproducible metabolome data and for the accumulation and compilation of the data. Analysis of relationships between metabolite profiles and internal perturbations is required as the references for diagnosis, medical treatment and drug design [90,91].

7. Application of metabolome in CC

One of the advantages of metabolomics is its ability to analyze metabolites from any source and regardless of origin. Dr. Masaru Yoshida has been using metabolome analysis to discover new biomarkers for gastroenterological diseases. This step is considered as early diagnosis method for early stages of CC based on metabolome profiles, and he used small amounts of blood in this analysis. On the other hand, Dr. Sen Takeda developed a new technique by collecting both mass spectrometry and machine-learning for cancer diagnosis. He presented a method for the clinical diagnosis of cancer using electrospray ionization and machine-learning called the dual penalized logistic regression machine [92]. The toxigenic *Bacteroides fragilis* (ETBF) correlated with bowel disease which leads to CC. The metabolome profile through gas and liquid chromatography associated with mass spectra were applied to provide more details in reconstruction of vesicle metabolic pathways involved. The metabolic activity of ETBF of the outer membrane vesicles provides their similarity to micro reactors [93]. Furthermore, the gastrointestinal microbiota and metabolome are extremely and dramatically changed in CC which indicates to the pathological condition or CC state. In CC, there are pathological changes in the intestinal microbiome, metabolome and epithelium. These changes are correlated with specific types of dietary bioactives, prebiotics or probiotics in CC. The metabolome analysis discussed in details the effects of diet, host and microbiota in CC to provide the development personal strategy of human nutrition and research of nutrition [94]. There were a total of 728 distinct metabolites recognized from colonic tissue and stool matrices. There are 19 metabolites significantly distinguished CC from adjacent mucosa in CC patients. The metabolic pathway investigation exhibited significant perturbations of short-chain fatty acid metabolism, fructose, mannose, galactose metabolism, glycolytic, gluconeogenic and pyruvate metabolism [95]. There are 225 metabolites were observed in all four cell lines found. There are 67 of these molecules attack CC from ovarian cancer cells. Metabolic maps reveal an elevation in tricarboxylic acid cycle and lipid metabolism in ovarian cancer cell lines. There are an increase was observed in β-oxidation and urea cycle metabolism in CC cell lines [96].

There is a decrease in glutathione disulfide level while an increase was observed in reduced glutathione/glutathione disulfide ratio after check of 110 metabolites reported in metabolome profile in CC incidence and progress. These results obtained an indication that CC increases pentose phosphate pathway flux and preserve reduced glutathione levels in CC cells [97]. In an avian study, 80 metabolites were detected in CC incidence and progress by using nuclear magnetic resonance of different chickens tissues such as liver, kidney, spleen, plasma, colon, cecum, ileum, pectoral muscle and brain but there are only 8 core metabolites in every matric [98]. The early diagnosis of CC can be achieved by using CC biomarkers depend on circulating metabolites. Researches based on external population are required to evaluate and calculate the clinical benefits of CC biomarkers [99].

8. Conclusion and recommendations

Natural products are very important in preventing the CC in humans and animal models due to its protein disulfide manipulation concepts which plays very important and vital role through physiological process inside the body. Both natural products and hormones play very important role in regulating physiological process especially in CC cases, so it's very important to use both to regulate enzyme balance and

consequently the physiological status, and its import of both to prevent CC cases. Metabolome must become generally available in hospitals as a tool of diagnosis, as soon as further technical developments reduce the size and price of analytical tools as well as the cost of a sample analysis.

To protect against CC; I recommend to: (1) Using natural products and hormones to protect to be happen against CC. (2) Applying regular body fluid (urine, serum or plasma) check through metabolome technique every 3 months. (3) Making treatment of CC consistent with the patient's monthly routine report estimated by metabolome technique. (4) Offering encouragement to normal and CC cases to adhere to metabolome report schedule for both protective and treatment.

Conflict of interest statement

The author declares that there is no conflict of interest.

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