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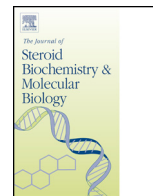
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Review

Environmental epigenetics and phytoestrogen/phytochemical exposures

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ABSTRACT

One of the most important environmental factors to promote epigenetic alterations in an individual is nutrition and exposure to plant compounds. Phytoestrogens and other phytochemicals have dramatic effects on cellular signaling events, so have the capacity to dramatically alter developmental and physiological events. Epigenetics provides one of the more critical molecular mechanisms for environmental factors such as phytoestrogens/phytochemicals to influence biology. In the event these epigenetic mechanisms become heritable through epigenetic transgenerational mechanisms the impacts on the health of future generations and areas such as evolutionary biology need to be considered. The current review focuses on available information on the environmental epigenetics of phytoestrogen/phytochemical exposures, with impacts on health, disease and evolutionary biology considered.

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1. Introduction

Endocrine disruptors are present in the environment from both synthetic and natural origins and have been shown to influence the physiology and development of organisms. These compounds interfere with the actions of endogenous hormones at several physiological levels [1]. Although progressive accumulation of synthetic endocrine disruptors in the environment has altered the ecological balances in natural populations and affected human health [2], nutritionally derived natural compounds provide a much more historical and quantitative exposure. Synthetic endocrine disrupting compounds are present in cosmetics, food containers, packaging materials, toys, agrochemicals and in nearly all manufactured products for humans [2–4]. However, alterations in nutritional habits and food composition provide one of the most common exposures for endocrine disrupting chemicals [2]. For example, the recent

nutritional change in the incorporation of soy-derived products into human diets has dramatically increased the consumption of plant derived chemicals [5].

Plant produced compounds (secondary metabolites) with estrogenic actions in animals are known as phytoestrogens [6,7]. Phytoestrogens are readily available in the environment in food items consumed by animals [7,8]. These compounds are polyphenolic structures similar to the estradiol molecule and have the ability to trigger estrogenic activity through estrogen receptor signaling pathways [9]. Phytoestrogens have been shown to produce physiological and developmental effects in animals [10]. Phytoestrogens are classified as flavonoids, cumestans, lignans and stilbens, with flavonoids (or isoflavones) being the most prevalent in dietary sources [5,9,11] (Table 1). However, plant derived chemicals (phytochemicals) that do not contain estrogenic activity are not phytoestrogens and should be termed phytochemicals. The problem with categorizing classes of compounds as phytoestrogens is that many do not contain estrogenic activity and should be classified as phytochemicals [12]. Therefore, the nomenclature in the field is currently problematic and needs to specifically assess estrogenic or endocrine disruptor activity of individual compound prior

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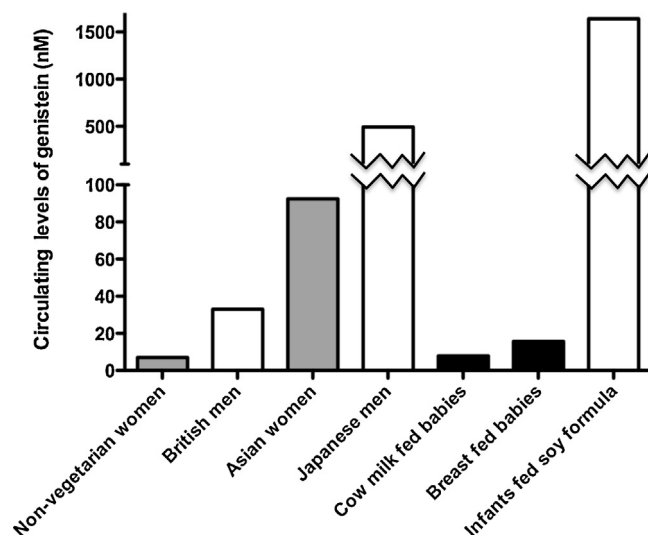


Fig. 1. Cross-studies comparison of circulating levels of genistein among different human groups. Gray bars indicate genistein serum concentrations in nM. White bars indicate genistein plasma concentrations in nM. Black bars indicate values extrapolated to nM concentrations of genistein from relations of isoflavone plasma concentrations in ug/L between differentially fed infants. Values were obtained from reviews in the literature [5,24].

to classification as phytoestrogens. The current review attempts to use the term phytoestrogen and phytochemicals appropriately.

The identification of phytoestrogens as having estrogenic or reproductive effects in animals dates back to observations from farmers in New Zealand regarding ewes becoming infertile after eating clover [13,14]. The same effect was further reported in cattle [15]. The fertility of captive cheetahs has also been shown to be affected by dietary consumption of soy [16]. Since then, reproductive effects of exposure to flavonoids have been reported in laboratory animals ranging from disruption of estrous cycle, sexual behavior, testis function, ovarian function and female reproductive tract function to early developmental effects [17]. In particular, dietary exposure of flavonoids have been shown by several studies to produce significant reproductive effects in rodents [18–26]. Interestingly, dietary intake of phytoestrogens by laboratory animals has also been shown to be high, with studies showing estrogenic effects derived from the consumption of some commercial mouse diets [27–30].

A number of epidemiological and laboratory studies have been performed with phytochemicals in the past 40 years due to their potential to affect human health through nutrition [31]. One of the main concerns is that soy products have become an important component of food products in adult and infant human diets in recent years [32]. Variable amounts of isoflavones are consumed by human populations in different regions of the world [24,33]. For example, isoflavone consumption in Asian countries (25–100 mg/day) is much higher than in western countries, such as the UK, with daily consumption below 1 mg [34]. Consequently, plasma levels of the phytoestrogens vary among western and eastern countries. For example, plasma levels of the phytoestrogens genistein and daidzein are more than 10-fold higher in Japanese men than in British men [35,36], Fig. 1. Serum levels can reach concentrations of isoflavones after a soy rich meal with estrogenic activity well above the levels of endogenously circulating hormones [37]. In regards to the potency, physiologically relevant concentrations of some phytoestrogens such as genistein, daidzein or cumestrol are able to stimulate the transcriptional activity of both estrogen receptors (in a cell based transcription assay) to the same or greater levels as synthetic compound such as diethylstilbestrol (DES), bisphenol A (BPA), dichlorodiphenyltrichloroethane (DDT), methoxychlor, or

tamoxifen [38]. The modes of action of phytoestrogens include several other pathways in addition to binding to estrogen receptors. These are rapid cellular responses (AMP-activated protein kinase, mitogen-activated protein kinase and phosphoinositide 3-kinase pathways), antioxidant action, tyrosine kinase inhibition, peroxisome proliferator-activated receptor gamma (PPAR) mediated action [5] and binding to the non-classical estrogen receptor GPR30 or the aryl hydrocarbon receptor [17]. In addition, the role of phytoestrogens as selective estrogen receptor modulators (SERMs) such as tamoxifen should not be dismissed, given the ability of phytoestrogens to bind to the ER and produce tissue-specific actions that depends on the presence of cofactors that helps modulate the interaction [39]. For example, nude mice with a low-dose genistein exposure can negate the effect of tamoxifen of reducing MCF-7 breast tumor cells growth [40]. An important aspect of exposure to phytochemicals is potential combination effects with other hormonally active compounds [41,42].

2. Physiological impacts

Human studies show that isoflavone consumption has a variety of physiological effects. Intake of isoflavones has been suggested to alter sex hormone concentrations in adults [43,44] and children [45]. For example, soy isoflavone consumption by premenopausal women is associated with increased circulating luteinizing hormone (LH) and follicle stimulating hormone (FSH), and increased menstrual cycle length [46]. In postmenopausal women, changes in sex hormone-binding globulin levels have been observed [47]. A recent study found an association of high content of isoflavones in the blood with precocious puberty in Korean girls [48]. Other studies in women correlate consumption of phytoestrogens with increased sexual arousal [49], increased risk for uterine fibroids [50], and abnormal uterine bleeding [51]. Recently, a panel of experts has reviewed the literature on the use of soy in infant formulas due to the concern raised by several studies regarding adverse effects later in life [32]. In men, one study suggests that increased hypospadias could be related to a high developmental exposure to phytochemicals/phytoestrogens from a vegetarian maternal diet during gestation [52]. High intake of dietary isoflavones has been correlated with low sperm numbers in men from subfertile couples [53]. In addition to reproductive effects, consumption of flavonoids is thought to have a protective effect against cancer in specific organs [54], including breast cancer in humans [55]. However, recent studies suggest that this protective effect of flavonoids against cancer would only occur if the exposure is during childhood/adolescence [56,57].

One of the main concerns about high phytoestrogen/phytochemical diet consumption in humans is the effects on early developmental stages, such as the effects on infants consuming soy-based formulas. The effects of high consumption of isoflavones by pregnant mothers in uterus, placenta or breast milk are also a concern in terms of their influences on the developing embryo. Circulating plasma concentrations of isoflavones is considerably high in infants consuming soy-formula, being 50–100 times higher than levels in pregnant women, 10–50 times higher than in Asian women, 100–700 times higher than in non-vegetarian US women [5,24] (Fig. 1). The equivalent estrogenic activity in these infants is 13,000–22,000 higher than normal endogenous estrogen levels [5]. Maternal exposures are also crucial during embryogenesis, when the fetal microenvironment is susceptible to maternal influences due to dietary compounds [58] or hormonal changes [59]. One important maternal exposure route is through the placenta. It has been shown that genistein aglycone can cross the placental barrier and reach the fetal brain in rats [60,61]. Effects in the early embryo are also mediated by physiological

Table 1
Common phytochemicals and their classification.

Common phytoestrogens	Chemical classification	Nutritional source
Genistein	Flavonoid	Grains, fruits, vegetables [7,8]
Daidzein	Flavonoid	Grains, fruits, vegetables [7,8]
Quercetin	Flavonoid	Grains, fruits, vegetables [107]
Resveratrol	Stilben	Grapes, itadori tea, peanut roots [11]
Coumestrol	Coumestrol	Grains and vegetables [108]
Lignans	Lignans	Seeds, cereals, grains, vegetables and fruits [109]

alterations that dietary isoflavones can promote in the uterus. For example, in both mice and rats it is well reported that dietary genistein increases uterine wet weight [20,21,25,30,62] and alters uterine gene expression [20,21,30,62,63]. In addition, it has also been reported that the uteri of genistein treated females are not capable of supporting normal implantation [64]. Another route of maternal exposure is lactation. Isoflavones have been detected in breast milk from mothers consuming a soy-based beverage and in the urine of infants breast feeding this milk [65]. Therefore, maternal high soy-based diet could be an important route of early postnatal exposure to phytoestrogens (Fig. 1). However, studies in rats show that lactational transfer of genistein to rat pups is limited [60,66].

Combined observations suggest perinatal exposure to phytoestrogens appears crucial in impacting developing embryos and influencing adult phenotypes. Embryos developmentally exposed to phytoestrogens present reproductive abnormalities in adults such as aberrant estrous cycles, early reproductive senescence, mammary adenomas and adenocarcinomas [60], altered uterine gene expression [22] and altered response to estrogen in tissues such as uterus [21,25], tibia and liver [25]. Studies in mice and rats have also shown that a perinatal high dietary exposure to isoflavones advances sexual maturation in females [19,23,67] and has differential effects in body weights between males and females [19,23]. Due to the long lasting effects of developmental exposures

to isoflavones on abnormal phenotypes and gene expression, epigenetic mechanisms need to be considered.

3. Environmental epigenetics

The relationship between the action of endocrine disruptors and epigenetic modifications is becoming well established [68]. Examples of epigenetic alterations that occur after exposure to synthetic endocrine disrupting compounds include effects of exposure to bisphenol A [69,70], diethylstilbestrol [71], butyl paraben [72], airborne polycyclic aromatic hydrocarbons [73] and vinclozolin [74]. Epigenetics is defined as molecular factors and processes around the DNA that regulate genome activity independent of DNA sequence, and are mitotically stable [75]. Such molecular factors and processes include histone modifications, chromatin structure, DNA methylation or hydroxymethylation and non-coding RNAs. Research has expanded regarding the role of environment in producing epigenetic modifications that has developed a better understanding of epigenetic mechanisms [76]. For example, the intricate relation between histone modifications and other mechanisms of epigenetic modification, such as DNA methylation, are now known to be fundamental to the establishment of epigenetic patterns [76,77]. Important molecular interactions involved in chromatin replication are now understood [78]. Crucial factors that participate in the process of DNA methylation programming are

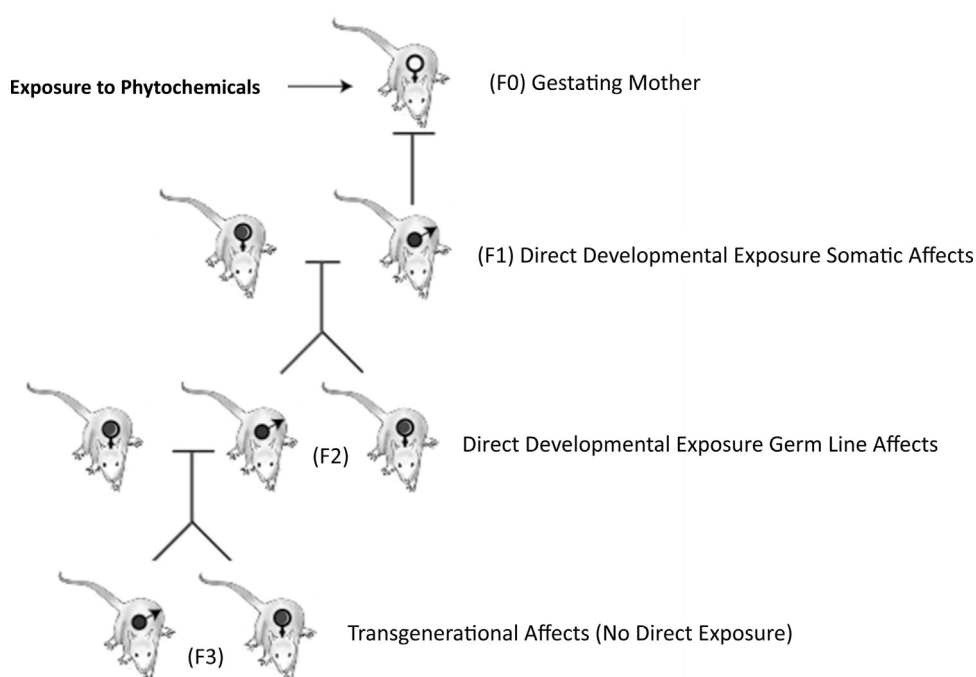


Fig. 2. Transgenerational transmission of information through the male germline for the directly exposed F0 generation female, F1 generation fetus, F2 generation germline affects and the transgeneration F3 generation affects in the absence of direct exposure.

now known that have lead to a better understanding the developmental mechanisms of DNA methylation and demethylation [77]. Importantly, a number of studies have reported that interference of the process of germ line programming of DNA methylation patterns can lead to altered DNA methylation states in future generations [75,79].

Evidence for the epigenetic actions of natural endocrine disruptors and phytochemicals such as flavonoids has also been described in recent years. The first study to show an epigenetic effect of flavonoids was performed with administration of the phytoestrogens coumestrol and equol to newborn mice which increased DNA methylation at the proto-oncogene *H-ras*, resulting in its inactivation [80]. DNA methylation patterns have been shown to be altered in 8-week-old mice after consumption of high doses of the phytoestrogen genistein [81]. Genistein can have a protective effect in prostate cancer via histone demethylation and/or acetylation and chromatin remodeling of tumor suppressor genes, resulting in their activation [82,83]. Treatment of human renal carcinoma cell lines with genistein up-regulate the tumor suppressor gene *BTG3* through decreasing promoter methylation [84]. A thorough analysis of genistein repression of human breast cancer and pre-cancerous cultured cells has been published [85]. The study showed genistein promotes hypomethylation of the E2F-1 sites in the *hTERT* (human telomerase reverse transcriptase) promoter which leads to increasing binding of E2F-1 and inhibition of *hTERT* transcription. Genistein also reduced expression of *Dnmt1*, *Dnmt3a* and *Dnmt3b* in these breast cancer cells and changed methylation in H3K9 and H3K4 histones at the *hTERT* promoter [85]. Recently, genistein and daidzein have been shown to induce DNA demethylation in the promoter regions of *BRCA1*, *GSTP1*, *EPHB2* and *RASSF1A* in human prostate cancer cell lines [86]. Genistein has also been shown to interfere with DNA methylation in differentiated ES cells after the process of *de novo* methylation [87]. In endometrial stromal cells genistein has been shown to promote DNA demethylation of the steroidogenic factor 1 (*SF-1*) promoter [88]. Changes in methylation in two classes of repeat elements (*SINEB1* and *SINEB2*) have also been reported in bone marrow after a prenatal exposure to dietary genistein, with a corresponding effect on the pattern of red blood production [89]. A summary of the effects of these phytoestrogens on epigenetic marks is shown in Table 2.

In addition to these direct exposure epigenetic effects, it has been hypothesized that phytoestrogens could affect the establishment of methylation patterns in the offspring due to a multigenerational direct maternal exposure [10,90]. Evidence for this was reported by different laboratories. In the agouti mouse model, maternal dietary supplementation with either methyl-donors or genistein [91] showed to inhibit a bisphenol A-induced hypomethylation of interstitial A particle (IAP) repeat elements upstream of the *A^{vy}* allele. Methylation changes in that region correlate with coat color changes. Gender specific changes in *Acta1* gene methylation have been shown as a response to a diet rich in the phytoestrogens genistein and daidzein in mice [19]. Neonatal exposure of female mice to high levels of genistein results in tissue-specific hypermethylation of the gene *Nsbp1* in the uterus [71].

The fact that exposure to flavonoids is capable of altering epigenetic states in the F1 generation leads to the speculation that it could also induce epigenetic changes in further generations. Trans-generational transmission of environmentally induced epigenetic modifications and phenotypes is a recently identified phenomena [92] that has been replicated in a number of laboratories with diverse environmental compounds. Previous research has shown that a developmental exposure to vinclozolin can affect developmental processes in the embryonic testis, which can produce an increase in spermatogenic cell apoptosis in the adult [93].

Table 2
Phytoestrogen induced epigenetic modifications.

Increased DNA methylation in <i>H-ras</i> proto-oncogene in pancreas after treatment with coumestrol or equol	Lyn-Cook et al. [80]
Alterations in DNA methylation in prostate after exposure to genistein, detected by mouse differential methylation hybridization	Day et al. [81]
Maternal dietary genistein supplementation of mice during gestation shifted the coat color of heterozygous viable yellow agouti (<i>Avy/a</i>) offspring toward pseudoagouti, which was associated with increased DNA methylation in an IAP particle upstream of the Agouti gene	Dolinoy et al. [110]
Maternal genistein consumption prevents in the offspring's kidney DNA hypomethylation of an IAP particle of the gene <i>Cabp</i> induced by bisphenol-A	Dolinoy et al. [91]
Genistein induced the expression of tumor suppressor genes p21 (<i>WAF1/CIP1/KIP1</i>) and p16 (<i>INK4a</i>) and DNA hypomethylation of the p21 promoter in an androgen-sensitive (LNCaP) and an androgen-insensitive (DuPro) human prostate cancer cell line. Genistein increased acetylated histones 3, 4, and H3/K4 at the p21 and p16 transcription start sites	Majid et al. [83]
Genistein activated tumor suppressor genes by modulating histone H3–Lysine 9 (H3–K9) methylation and deacetylation at their promoters in prostate cancer cells	Kikuno et al. 2008 [82]
Perinatal consumption of a diet rich in genistein and daidzein produces gene specific changes in DNA methylation in <i>Acta1</i> in liver.	Guerrero-Bosagna et al. [19]
Neonatal exposure of female mice to high levels of genistein results in tissue-specific DNA hypermethylation of the gene <i>Nsbp1</i> in the uterus	Tang et al. [71]
Genistein upregulates <i>Btg3</i> expression through DNA hypomethylation of that gene in human renal carcinoma cell lines	Majid et al. [84]
Genistein promotes DNA hypomethylation of E2F-1 sites in <i>hTERT</i> in breast benign derived cell and breast cancer cells	Li et al. [85]
Genistein upregulates <i>Btg3</i> expression through its DNA hypomethylation of that gene in prostate cancer tissue and cell lines	Majid et al. [111]
Genistein or daidzein induced DNA demethylation in promoter regions of the genes <i>BRCA1</i> , <i>GSTP1</i> , <i>EPHB2</i> and <i>RASSF1A</i> in human prostate cancer cell lines	Vardi et al. [86]
Prenatal exposure to dietary genistein promotes changes in DNA methylation in the repeat elements class <i>SINEB1</i> and <i>SINEB2</i> in bone marrow	Vanhees et al. [89]
Genistein perturbed DNA methylation patterns of differentiated ES cells after <i>de novo</i> methylation	Sato et al. [87]
Genistein promoted DNA demethylation of the steroidogenic factor 1 (<i>SF-1</i>) promoter in endometrial stromal cells	Matsukura et al. [88]

This vinclozolin-induced spermatogenic alteration was transgenerationally transmitted from the F1 generation, which was developmentally exposed, to the F2, F3 and F4 generations [92,94,95]. In the event a gestating female is exposed, the F0 generation female and F1 generation fetus are directly exposed, the germline that will generate the F2 generation is also directly exposed, and it is not until the F3 generation that a transgenerational affect in the

absence of direct exposure can be deduced, Fig. 2. More extensive analyses determined that vinclozolin-induced epigenetic transgenerational alterations are produced in F3 generation sperm DNA [96]. Independent research groups have now shown the phenomena of environmentally induced epigenetic transgenerational inheritance of adult onset diseases. For example, BPA has been shown to promote transgenerational testis abnormalities [97], dioxin has been shown to promote transgenerational uterus abnormalities [98], and vinclozolin has been shown to promote imprinted gene DNA methylation changes [74]. A recent study has shown that environmental toxicants such as jet fuel, dioxin, a mixture of BPA and phthalates, and a mixture of pesticides have the ability to promote the epigenetic transgenerational inheritance of diseases [99]. Some pharmaceutical agents such as thyroxine and morphine have also been shown to promote behavioral abnormalities observed from the F1 to F3 generations [100]. Chemotherapy has also been shown to produce transgenerational effects, including despair-like behaviors, delivery complications, reduced primordial follicle pool and early loss of reproductive capacity [101]. In addition to synthetic chemicals, nutritional factors have also been shown to induce epigenetic transgenerational inheritance of disease states [102,103]. For example, caloric restriction has been shown to promote transgenerational metabolic disease phenotypes [103], and high fat diets have been reported to promote transgenerational adult onset metabolic disease and obesity [104,105]. Currently, no transgenerational studies have been reported with phytoestrogens or phytochemicals. Given the relevance of phytoestrogen exposure in humans and its known epigenetic actions the potential that phytoestrogen/phytochemical compounds promote epigenetic transgenerational inheritance of disease and phenotypic variation needs to be investigated.

In addition to the impacts of phytochemical exposures on health and disease, these compounds may have significant impact on the biology of most species. With the identification of environmentally induced epigenetic transgenerational inheritance phenomena [75], the ability of an environmental exposure to influence all subsequent generations after an individual or population exposure may have significant impacts on evolutionary biology [106]. For example, an exposure to an environmental compound promoted the epigenetic transgenerational inheritance of sexual selection phenotypes that would subsequently impact evolutionary changes [106]. In the event a populations phytochemical exposure [90] was altered and induced epigenetic transgenerational inheritance of phenotypic variation, subsequent natural selection events may occur in the population to promote an evolutionary change. Therefore, due to the potential transgenerational nature of the actions of the phytoestrogens/phytochemicals the impacts on evolutionary biology also need to be considered.

4. Conclusions

Phytochemicals are one of the largest classes of compounds humans are exposed to throughout life. Phytoestrogens are naturally available endocrine disruptors in the environment. More recently, humans have an increased exposure to these compounds due to nutritional changes in the variety of food items that are consumed. Given the diverse mechanism of action, the potency of these compounds, the impact of phytochemicals on disease, and the potential for combinatorial effects with other common synthetic toxicants, it will be fundamental in the future to increase the focus on epigenetic effects of phytoestrogens/phytochemicals. Perhaps most important will be to investigate potential transgenerational effects of exposure to phytoestrogens/phytochemicals. Given the natural occurrence of these compounds for animal consumption, it is critical to consider physiological effects in populations of wild

animals, as well as the ecological and evolutionary consequences of epigenetic changes triggered by phytochemicals.

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