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Review Article

Biological Properties and Uses of Honey: A Concise Scientific review

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ABSTRACT

The global prevalence of chronic diseases such as diabetes mellitus, hypertension, atherosclerosis, cancer and Alzheimer's disease is on the rise. These diseases constitute the major causes of death globally. Honey is a natural substance with many medicinal properties such as antibacterial, hepatoprotective, hypoglycemic, reproductive, and antihypertensive and antioxidant. This review presents findings that indicate honey may ameliorate oxidative stress in the gastrointestinal tract (GIT), liver, pancreas, kidney, reproductive organs and plasma/serum. Besides, the review highlights data that demonstrate the synergistic antioxidant effect of honey and antidiabetic drugs in the pancreas, kidney, and serum of diabetic rats. These data suggest that honey, administered alone or in combination with conventional therapy, might be a novel antioxidant in the management of chronic diseases commonly associated with oxidative stress. In view of the fact that the majority of these data emanate from animal studies, there is an urgent need to investigate this antioxidant effect of honey in human subjects with chronic or degenerative diseases.

Introduction

Honey is a natural product that has been widely used for its therapeutic effects. It is also one of the nature's wonders. It is nothing more than nectar gathered from the blossoms of many flowers by bees. Honey has been a common sweetener for foods and a powerful medicinal tool for centuries [1, 2]. It has been reported to contain about 200 substances. The composition of honey varies depending on the plants on which the bee feeds. Honey is composed primarily of fructose and glucose but also contains fructo-oligosaccharides and many amino acids, vitamins, minerals and enzymes [3, 4]. However, almost all natural honey contains flavonoids (such as apigenin, pinocembrin, kaempferol, quercetin, galangin, chrysin and hesperetin), phenolic acids (such as ellagic, caffeine, p-coumaric and ferulic acids), ascorbic acid, tocopherols, catalase (CAT), superoxide dismutase (SOD), reduced glutathione (GSH), Millard reaction products and peptides. Most of those compound works together to provide a synergistic antioxidant effect [5, 6]. Honey has had a valued place in traditional medicine for centuries [7, 8]. However, it has a limited use in modern medicine due to lack of scientific support [9]. For a long time, it has been observed that honey can be used to overcome liver, cardiovascular and gastrointestinal problems [10]. Ancient Egyptians, Assyrians, Chinese, Greeks and Romans employed honey for wounds and diseases of the intestine [11]. Since a few decades ago, honey was subjected to laboratory and clinical investigations by several research groups. The most remarkable discovery was the antibacterial activity of honey that has been mentioned in numerous studies [12]. Natural honey exhibits bactericidal activity against many organisms including Salmonella, Shigella, *Escherichia coli* [13, 14]. *Helicobacter pylori*[15]. The healing properties of honey can be ascribed to the fact that it offers antibacterial activity, maintains a moist wound environment that promotes healing, and has a high viscosity which helps to provide a protective barrier to prevent infection [16]. Research has also indicated that honey may possess anti-inflammatory activity and stimulate immune responses within a wound [17, 18] demonstrated anti-inflammatory effects of honey in human after ingestion of honey [19]. Honey, interestingly, has been shown to prevent reactive oxygen species (ROS)-induced low density lipoprotein (LDL) oxidation in some *in vitro* studies, thus exhibiting beneficial cardiovascular protection [20, 21]. Honey also had antineoplastic activity in an experimental bladder cancer [22].

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This article has reviewed important traditional and modern uses of natural honey in human and animal diseases.

Biological activities and effects of honey

Antioxidant properties of honey

Unlike synthetic compounds, honey represents a natural product that does not carry side effects which can be harmful to health. Among the compounds found in honey; vitamin C, phenol compounds, catalase, peroxides, glucose oxidase enzymes have antioxidant properties [23]. Various polyphenols are reported in honey. Some of the polyphenols of honey like Caffeic acid, Caffeic acid phenyl ester, Chrysin, Galangin, Quercetin, Acacetin, Kaempferol, Pinocembrin, Pinobanksin and Apigenin have evolved as promising pharmacological agents in the treatment of cancer [24].it was also observed that administration of honey with alcohol prevent to great extent the lesions caused by only chronic alcohol administration [25]. Honey also contains flavonoids and carotinoids. High levels of these indicators ensure a high level of antioxidants in honey. Antioxidant properties of honey act as an antidepressant during high emotional, physical and intellectual stress [26]. Moreover, honey has been associated with improved antioxidant capacity, modulation of the immune system, antimicrobial activities, influence on lipid values (through antihypercholesterolemic effects) and regulation of glycemic. [27]. Observed the protective role of honey against ochratoxin A-induced oxidative stress in liver and kidney in rats, and demonstrated that honey ameliorated the toxic effects of OA on histological and biochemical parameters in liver and kidney [28].The antioxidants have several preventative effects against different diseases like cancer, cardiovascular diseases, inflammatory disorders, neurological degeneration, wound healing, infectious diseases and aging [29]. The honey antioxidative activity has also been proven anti-inflammatory and antioxidant properties [30]. The honey antioxidative activity has also been proven in to assess the antioxidant activity of three varieties of honey from different botanical and geographical (Manuka honey from New Zealand, Acacia Honey from Germany and Wild carrot honey from Algeria). Manuka honey had the highest phenolic content with 899.09 ± 11.75 mg gallic acid/kg. A strong correlation between the antioxidant activities of honey and their total phenol contents has been noticed [31]. Also study was reported that the administration of honey with monosodium glutamate (MSG) improved histological changes in kidney induced by MSG in the negative control. It concluded that honey via its antioxidant activity has the ability to protect against MSG [32].Evidence indicates that honey can exert several health-beneficial effects such as gastroprotective [33], hepatoprotective [34], reproductive [35], hypoglycemic and antioxidant [36], antihypertensive [37], antibacterial [38], anti-fungal [39] and anti-inflammatory [40] effects .Honey has powerful immune system booster. Its antioxidant and antibacterial properties help to improve the digestive system [41]

Insulin-like action

Voiced that honey is good for diabetics. This is unlikely to find confirmation because of its high sugar content. However, it is better than products made with cane sugar. It revealed that insulin levels were lower when compared to the uptake of equal caloric values of other foods, but blood sugar level was equal or higher than in the other compared products shortly after eating [42].Some tests were carried out to confirm that honey reduced effects of diabetes on animals. Where reported that honey produces a lower glycemic response in both diabetic and non-diabetic rabbits [43].

It was also reported that in healthy individuals, the consumption of honey produced lower blood sugar readings than the consumption of the same quantity of sucrose [44].

Observations from the study of [45] show that camel milk and or the honey bee has a hypoglycemic effect on experimental diabetic rats. The consumption of honey decreases glycemic levels and blood lipids in healthy, diabetic and hyperlipidemic individuals [46].A study on mice suggests that honey improves glycemic control in streptozotocin-induced diabetic rat. The study showed that the combination of antidiabetic drugs, glibenclamide or metformin, with honey resulted in further reductions in serum concentrations of both glucose and fructosamine in STZ-induced diabetic rats [47].Another study on mice suggests that honey demonstrated that consuming natural honey with Metformin improves glycemic control and is more useful than consuming Metformin alone. The higher therapeutic effect of Ilam honey on lipid abnormalities than Tualang honey was also evident [48].Yet, another study was conducted to show the hypoglycemic effect of honey bee venom on alloxan induced diabetic male rats and treated the group that received honey bee venom in honey daily before their nutrition for four months. The results of this study revealed that glucose serum, triglyceride and total cholesterol level in treated group in comparison with the diabetic group was significantly decreased ($P< 0.01$). On the other hand, using bee venom causes an increase in insulin serum in comparison with the diabetic group ($P< 0.05$). These results suggested that honeybee venom (apitoxin) can be used as a therapeutic option to lower blood glucose and lipids in diabetic rats [49].

Hypotensive and blood regulatory actions

The role of oxidative stress in hypertension is a subject of much research interest. Oxidative stress is implicated in the pathogenesis of hypertension [50]. While some evidence also indicates that hypertension generates oxidative stress [51].These lines of evidence support a role of oxidative stress as an important determinant in the imbalance between vasoconstrictor and vasodilator mechanisms [52, 53]. The beneficial effects of antioxidants in ameliorating oxidative stress and suppressing or reducing elevated blood pressure in experimental and clinical studies further corroborate the role of oxidative stress in hypertension [54].The combination of diabetes mellitus and hypertension is associated with increased cardiovascular risk factors [55, 56].Besides other factors, evidence suggests that diabetes mellitus may exacerbate hypertension via increased oxidative stress[57] also study

revealed that the antioxidant effect of honey resulted in further reductions in blood pressure of diabetic SHR but not of diabetic [58].

Another study reported reduced glycosylated hemoglobin in the non-diabetic rats after chronic (52 weeks) honey supplementation [59].A similar beneficial effect of honey was reported in patients with impaired lipid metabolism [60,61].In diabetes, the antioxidant effect of honey may also be beneficial in lipid metabolism [62,63,64].(e.g., in inhibiting or preventing the oxidation of low density lipoprotein) [65]. A study that investigated the protective effect of honey and Nigella grains against methylnitrosourea-induced oxidative stress and carcinogenesis indicated that Nigella sativa grains reduced the elevated levels of MDA and nitric oxide (NO) in serum and produced a protective effect of 80%. On the other hand, the combination of honey and Nigella sativa abolished the increases in MDA and NO and exerted a protective effect of 100% against MNU-induced oxidative stress and carcinogenesis [66]. Other studies have also demonstrated the antioxidant effect of honey in serum as evidenced by the increased plasma NO metabolites in healthy sheep [67] and the increased GPx activity and NO in the serum of alloxan-induced diabetic rats [68].Other studies have also shown a significant increase in the level of plasma TG, HDL, and VLDL in the test group at the dose (1ml of honey was added to 10ml of drinking water given once every day) for 22 weeks. When compared with the control group ($P<0.01$). In contrast, there were significant decreases in the levels of plasma LDL and total cholesterol in the test when compared with the control group ($P<0.01$). Computed values of CVPI have shown a significant increase in the test values compared to that of the control ($P<0.01$). It is concluded that consumption of unrefined Nigeria honey significantly improved lipid profile and computed cardiovascular disease predictive index in male albino rats [69].Treatment with honey also showed protective effects on organs through the improvement the hematological and biochemical parameters (RBCs, WBCs, Platelets, ALT, AST, ALP, urea, Creatinine, Triglyceride, Total cholesterol, HDL and LDL). These results showed that honey may have a therapeutic protect effect organs during inflammatory diseases [70].

Antibiotic effect

It was demonstrated that honey either retained or demonstrated enhanced antibacterial property even when used in a dilute form. This suggested that apart from high sugar content there are other active components in honey which are responsible for its antibacterial properties. Later it was found that apart from other components, the effect of hydrogen peroxide made honey a potent antibacterial agent [71].

The results of the study of revealed that honey: its composition and quality vary greatly with the botanical source of nectar as well as environmental and climatic conditions. Depending on its quality, honey can contribute to the health and nutritional status of humans. These beneficial actions have been ascribed to its antimicrobial, anti-inflammatory and anti-oxidant potential. Interestingly, honey is gradually receiving attention as a complementary and or an alternative source of treatment in modern medicines. It is active against antibiotic-sensitive and antibiotic-resistant strains of micro-organisms and has the potential not to select for further resistant strains [72].Its antibacterial potentials even against multi-drug resistant bacteria, such as *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Acinetobacter baumanni* have been proved. Honey is well known for its anti-inflammatory and antioxidant capacities, which may be useful for the prevention of chronic inflammatory process like atherosclerosis, diabetes mellitus and cardiovascular diseases [73].

Anti-inflammatory action and wound healing property of honey

Honey reduces the inflammatory reaction even without the presence of an infection [74]. Monocytes are stimulated by honey *in vitro* to produce both pro-inflammatory and anti-inflammatory cytokines [75].There is a histological confirmation of tissue recovery with a minimal infection one week after the treatment in superficial wounds of the skin [76].Clinical observations clearly show that when honey is applied to a wound, less redness, less edema formation and less exudate oozing out occur and that there is less awareness of pain [77].

Another study mentioned that the time taken for complete repair of the wound(superficial burns) created by red hot pins was much less when honey was applied to it as compared to sucrose of same composition [78].It is also mentioned that infection experiment procedure was with additional artificial infection created by injecting *Staphylococcus aureus* two days prior to wounding. The wounds thereafter were dressed with honey, ampicillin ointment and saline as control. Results revealed that honey demonstrated the fastest rate of healing as compared to the other treatments and control [79]. It was reported that honey reduces the activities of cyclooxygenase-1 and cyclooxygenase-2, thus showing anti-inflammatory effects [80]. The present results suggest that honey accelerates the inflammatory reaction and initiates healing early on in the treatment process. [81]. reported that honey is used in moisturizing and nourishing cosmetic creams, but also in pharmaceutical preparations applied directly on open wounds, sores, bedsores, ulcers, varicose ulcers and burns. It helps against infections, promotes tissue regeneration, and reduces scarring also in its pure, unprocessed form. If applied immediately, honey reduces blistering of burns and speeds regeneration of new tissue. Many case histories are reported in the literature for human as well as veterinary medicine. applied cream three times per day made 9 of equal parts of honey, rye flour and olive oil. This cream has been successfully used on many sores and open wounds even gangrenous wounds in horses [82].It is also reported that external as well as internal wounds from operations become bacteriologically sterile within a few days and dry out. The simultaneous stimulation of tissue regeneration by honey reduces scarring and healing times. In addition to dressing

applied with honey do not stick to the wounds or delicate new skins. In many tropical field hospitals, where antibiotics and other medicines are scarce, honey has been employed successfully for a long time [83].

Effects on the reproductive system and fertility

These data suggest that honey may protect or ameliorate CS-induced testicular damage in rats via its antioxidant effect. The authors in one of their previous studies also reported that honey supplementation in normal rats improved Spermatogenesis [84].A recent study also demonstrated the beneficial effects of honey on sperm motility and morphology in rats [85]. A study by Abdul-Ghani and colleagues also indicated that honey supplementation in rats caused increased epididymal sperm count and improved the activity of testicular marker enzymes for spermatogenesis, as evidenced by increased sorbitol dehydrogenase and reduced lactate dehydrogenase [86]. Available data in ovariectomised female rats also suggest that honey may produce beneficial effects in female reproductive organs [87]. A similar beneficial effect of honey on oxidative stress was also reported in human subjects. A study investigated the effects of 8-week honey supplementation on seminal plasma cytokines, oxidative stress and antioxidants in male road cyclists during intensive cycling training [88]. The study found that honey supplementation significantly increased the concentrations of seminal SOD, CAT and TAS. This antioxidant effect of honey was also associated with lower elevations in the seminal IL-1beta, IL-6, IL-8, TNF-alpha, ROS and MDA levels [88]. Another study on mice the results showed significant ($P<0.05$) increase in oocyte maturation, fertilization by *in vitro* fertilization (IVF) and cleavage of the oocyte by IVF between the three groups. Also, there is a significant increase in sperms motility. Decreased percentage of dead sperms between control and treated in two different doses i.e. 1.2 and 1.8 g/kg body weight for 35 days groups and a significant decrease in abnormalities of sperms in mice between the three groups [89].A preliminary clinical study was conducted involving post-menopausal women aged 45 to 65 years. Hundreds healthy post-menopausal women were given 20 g/day of Tualang honey and followed up for 6 months. The results showed that there were significant changes in the diastolic blood pressure, serum total cholesterol and LDL levels between the two groups after 6 months. Other clinical findings and laboratory investigations were not significant. Honey cocktail has slightly better effects than Tualang Honey in improving the physiological profile of post-menopausal women [90].

Effects honey on the kidney and liver

The daily intake of natural bees honey at a dose of 2.5g/Kg body weight resulted in sufficient amelioration against the hazard effects of food additives as indicated by the observed improvement in all tested biochemical parameters of kidney functions [91].A study revealed that Indian honey protects the liver against oxidative damage and it could be used as an effective hepatoprotector against APAP-induced liver damage [92].

It is observed that the administration of natural honey to the rats diminished hepatotoxicity and nephrotoxicity induced by lead acetate in the male rat [93]. Furthermore other study reported that simultaneous supplementation of honey with the administration of lead for 7 weeks reduced the lead-induced increase in the level of zinc in blood, liver, and kidney, and a decrease in blood hemoglobin [94].

Honey improved the disrupted liver biochemical markers and alleviated the increase of lipid peroxidation, where the use of honey minimized the toxic effect of AlCl3 in the liver by alleviating its disruptive effect on the biochemical and molecular levels [95].Also observed that administration of honey with doxorubicin prevent to great extent the histopathological changes and the structure of liver and kidney cells appearance were similar to control group[96,97].A study conducted on mice results suggested the harmful side effects of cadmium on liver and kidney, and it was concluded that honey via its antioxidant activity has the ability to protect against cadmium induced hepatotoxicity and nephrotoxicity [98].It is also observed that honey was effective in alleviating amikacin nephrotoxicity in rats [99]. Honey was reported to attenuate the hematological, biochemical and histological effects induced by gentamicin [100], a similar observation was reported by [101] who insured the nephroprotective effect of honey in albino rats. Gentamicin induced nephrotoxicity was insured by the pathological change in the biochemical and histological parameters in albino rats exposure to gentamicin, the treating by honey for sufficiently long duration reduced the gentamicin-induced nephrotoxicity. Similar findings were reported by [102].It was observed honey effective in alleviating Ibuprofen toxicity in the liver. The use of honey before paracetamol-induced nephrotoxicity resulted in a significant improvement in all evaluated parameters (urea and creatinine). Honey rendering most of the disturbed parameters to their normal levels [103].A study showed that the administration of paracetamol alone to the experimental rats caused a significant increase in serum activities of the liver enzymes (AST, ALT and ALP). The administration of honey was found to exhibit protective characteristics against paracetamol-induced liver injury as evidenced by the ability of honey to mitigate the increase in serum activities of the liver enzymes Concentration in rat exposed to paracetamol [104-106].It is also reported the protective effect of honey on cadmium induced toxicity, treatment of CdCl2-intoxicated animals with honey showed a decrease in the harmful effects of Cd by restoring hematological and biochemical changes [107].The ability of honey to prevent cadmium induced hepato-nephrotoxicity in rats was also reported by some authors [108-112]. Results showed that honey significantly reversed changes in serum levels of AST, ALT, MDA, SOD, total protein and also histopathological changes produced by anti-tubercular drugs; honey has significant prophylactic and therapeutic value against anti-tubercular drugs induced hepatotoxicity [113]. A study reported the protective effect of Nabk honey against pathological effects of penicillin and streptomycin on histological structure and functions of guinea pigs liver, treatment of animals with Nabk honey at dose 600

mg/kg for 30 days decreased these histopathological changes, the structure of liver and hepatocytes appearance was more or less similar to control group as well its function when compared to the control guinea pig [114].Also, the results showed that administration of nabc honey was able to modulate the affected values of the biochemical parameters, induced by qat, similar to the control values [115].A study showed that Honey bee-treatment significantly decreases blood glucose level in diabetic rats. TC, TG, LDL, VLDL are significantly ($p<0.05$) decrease whereas HDL significantly increase ($p<0.001$). The SGPT, SGOT and CRP were significantly decreased ($p<0.05$) after were daily injected by (65 mg/kg BW) with Honey [116]. A study reported that bee honey and royal jelly could be used as dietary preventive natural products against subchronic cisplatin- induced renal injury [117].

Effects of honey on the immune system

It has been suggested that the consumption of honey can exert several beneficial effects on the human immune response and on its associated mechanisms. In fact, honey has been reported to promote the multiplication of human peripheral blood B- and T-lymphocytes and the activation of neutrophils under conditions of cell culture [118]. In monocytic cell line culture, honey has been shown to stimulate the release of inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin-1β and interleukin-6 [119], which are involved in triggering a number of functions of the immune response to infection [120]. Moreover, in mice, it has been found that the intake of a honey-supplemented diet stimulates the production of antibodies during the primary and secondary immune responses against thymus-dependent and -independent antigens [121].

Other benefits of honey

The scarcity and desirability of bees honey connected it to divinity and Holy Koran very early in human history. Much of the traditional medicinal or nutritional uses of the honeybees have been continued up to now, but very few of them have seen scientific confirmation.

Nutritional benefits

It is reported that honey is said to facilitate better physical performance and resistance to fatigue, particularly for repeated effort; it also promotes higher mental efficiency. It is therefore used by both the healthy and the sick for any kind of weakness, particularly in the case of digestive or assimilative problems. Improved growth of non-breast fed newborn infants, improved calcium fixation in bones and curing anemia and anorexia may all attribute to some nutritional benefit or stimulation from eating honey [122].

Benefits to the digestive apparatus

Studies have reported successful treatment of various gastrointestinal disorders. Honey is said to improve food assimilation and to be useful for chronic and infective intestinal problems such as constipation, duodenal ulcers and liver disturbances [123].

Benefits to the respiratory system

Study reported that in temperate climates and places with considerable temperature fluctuations, honey is a well-known remedy for colds and mouth, throat or bronchial irritations and infections. The benefits, apart from antibacterial effects, are assumed to relate to the soothing and relaxing effect of fructose [124].

Benefits to eye disorders

Study reported that clinical cases or traditional claims that honey reduces and cures eye cataracts, cures conjunctivitis and various afflictions of the cornea if applied directly into the eye [125]. A study investigated and compared the antioxidant effects of honey and conventional treatment in alkali injury on the eyes of New Zealand White rabbits [126].

Ayurvedic medicine

The use honey predominantly as a vehicle for faster absorption of various drugs such as herbal extracts. Secondarily, it is also though to support the treatment of several more specific ailments, particularly those related to respiratory irritations and infections, mouth sores and eye cataracts. It also serves as a general tonic for newborn infants, the young and the elderly, the convalescent and hard working farmers [127].

It is reported that there are some authors or scientists considered honey as food, rather than a medicine, this attributes to that, most of the above mentioned benefits, at least for internal use, can most likely be described to nutritional effects of some kind. On the other hand our scientific understanding of cause and effect, typically only confirmed if a single compound measurably affects a well defined symptom, if far too limited to explain possibly more complex and subtle, particularly synergistic interactions [128].

Energetic and non-energetic nutrients of honey

Studies stated that as food, honey is mainly composed of the simple sugars fructose and maltose, which form the basis of almost all indications on how, when and why to use it. The main consideration is the fact that honey provides immediately available calories, from which it derives its energy value for healthy and sick people: quick access to energy without requiring lengthy or complicated digestive action. The same direct absorption also carried a risk of pathological sugar metabolism such as diabetes and obesity. Considering the non-energetic nutrients, sometimes honey is recommended because of its content of other nutrients like vitamins and minerals, but their quantity that it is unrealistic to think they can provide any significant supplement in a deficient diet [129].

Antibacterial activity of honey

Honey and beehive-related substances have been used as antiseptic agents (e.g., propolis) since at least the time of Aristotle [130].Despite the evident antimicrobial capacity of honey, as determined by its effective inhibition of bacterial and fungal proliferation and growth, there does not seem to be

any clear-cut cause, suggesting that it could correspond to a combined or synergic effect of the antioxidant compounds present [131].With regard to the antibacterial activity, it has been recently determined that extracts of unifloral honeys from the endemic Chilean tree, Quillay (Quillaja saponaria), which contain several natural phenolic compounds, show antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella typhi*, *Streptococcus pneumoniae* type β, and *Vibrio cholerae*, and antifungal activity against *Candida albicans* [132].

It is also reported that in the normal honey antibacterial activity attributed to high sugar concentration and acidity in the same (pH range 3.5 to 5.0). Yet, since also diluted honey has shown antibacterial activity, the active ingredient was attributed to an elusive substance generically termed `inhibin`` much of this activity was later attributed to hydrogen peroxide (H_2O_2) and responsible enzyme, glucose oxidase is basically inactive in concentrated normal honey. The biological significance of such a mechanism arises from the requirement to protect immature honey (with high moisture content) inside the colony until high sugar concentrations are achieved [133]. Also reported that antibacterial activity varies greatly between different types of honey In addition to glucose oxidase, honey seems to contain other mostly unknown substances with antibacterial effects, among which are polyphenols. However it has been well demonstrated that most of antibacterial activities of the honey are lost after heating or prolonged exposed to sunlight [134].

Conflict of interest: We declare that we have no conflict of interest.

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