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Effects of *Myrtus* and *Nigella sativa* extracts on performance and metabolism of rats: A review

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Abstract
In the contemporary world due to technological development the human life has become vulnerable and more at risk because now the diseases are more complicated. Similarly the causative agents, particularly the viruses, have now become more complex due to mutation of their genetic material that results in more resistant and virulent strains. So to counter these diseases a strong immune system is required which can save the living body. Since medieval times the plants have been the main source of food, shelter, and to treat different diseases as well as enhancing the immunity status of both humans and animals. In every civilization the plant-based medicines or phytomedicine have been an important part of first aid. This review elaborates the importance of phytogenic substances i.e. myrtle plant and *Nigella sativa* by exerting positive effects on metabolism and particularly enhancing the immunity of rats which is used as a human model.

Keywords: Immunity, metabolism, phytomedicine, rat

1. Introduction

1.1 Significance of phytomedicines

The use of plants as medicine dates back to the ancient European, Asian and African civilizations. The use of herbs to treat different diseases is the oldest form of ethno-medical practice known to the human beings and this way of treatment has been an integral part of healthcare of every civilization because at that time it was the only available way of treatment. Since medieval times the herbs are being used to potentiate the immune system and to treat the diseases of humans and animals. In contemporary world the significance of phytomedicines is increased even more because of high prices, side effects, untoward and detrimental effects of synthetic medicines used in humans as well as in the animals to treat various diseases. It is interesting to know that many modern day drugs i.e. codeine, morphine, atropine, quinine, etc. are plant-based. These phytomedicines are unique in a way that these are organic and do not have any side effects if used within the recommended dose. The synthetic medicines have wide range of detrimental side effects whereas their prolonged and consecutive use can create serious health problems for humans as well as for animals. The phytomedicines can also be used as nutraceuticals, which is defined as the food items used to treat the diseases [1].

The phytomedicine contain chemicals compounds which are used as immunostimulants to potentiate the immune system by enhancing immunity status, by activating cytotoxic T-lymphocytes, and by releasing various cytokines toward antigen to achieve the optimum response [2]. It is interesting to know that, particularly in the under develop and developing countries, about 70%-80% people prefer to use plant-based drugs [3]. The polyphenols exhibit unique biological activity to trigger the signaling pathway, to initiate and to potentiate the immune system to effectively fight the antigens entering the body [4].

The world has badly been affected by the novel corona virus Covid-19 and killed millions of people throughout the world. The scientists throughout the world made vaccines of different brands against the delta strains of corona virus and effectively saved the people. The corona virus has ability to change its genetic material and make new strain, Omicron, now the scientists are trying to make vaccine which is effective against this strain. There is no treatment effective against the virus whereas supportive therapy and a strong immune system can only save living body against viral infection. In this regard polyphenols were considered effective Covid-19 protease inhibitors in trial where affectivity of medicinal plants was evaluated against Covid-19 Mpro which was performed through the exclusive technique of molecular docking. In the trial it was noted different phyto bioactive compoundse. gapiin, rutin, diacetylcurcumin, and diosmi etc.

Effectively inhibited the protease enzyme, so it was concluded that the flavonoids might decrease the symptoms of Covid-19 infection [5].

1.2 Mechanism of action of phytomedicine

Generally the mode of action of phytomedicines includes diuretic, antihypertensive, anti-diabetic, immuno potentiating, anti-microbial, gastro protective, antioxidant, anti-inflammatory, etc. However exact mechanism of action is still not very much clear whereas it is supposed that it may be related to chemical composition of compound. It is considered when the phyto bioactive compounds are added to diet of animals they exert beneficial effects on the beneficial gut microbiota, decrease the microbial toxic metabolites, and show antimicrobial effects on the intestinal pathogenic bacteria [6]. In addition to this the phytochemicals also exhibit their mode of action through immunomodulation by increasing immune cells, modulation of cytokines and increasing the production of antibodies [7].

2. Reasons for using laboratory animals for research purpose

The rat is the most suitable laboratory animal to be used as a human model, and it is commonly utilized for therapeutic purposes. The animals are used by researchers to study human physiology and health related medical problems, as well as to guarantee the affectivity of novel clinical treatments. A portion of these issues are simply conceivable to research in living bodies and whenever there is no other choice left the scientists use animals. The animals have biological similarity to human beings (the DNA of mice resembles almost over 98% to that of humans) and are susceptible to a large number of similar infections. The rats have short life cycles, permitting them to be examined throughout an extensive stretch of time or through various generations. Besides, the researchers can control animal's environmental factors (diet, temperature, lighting, etc.), which is almost difficult when human are under study. The most fundamental contention for utilizing animals is on the grounds that it would be unethical to intentionally subject the humans to health hazards to study how diseases develop.

3. *Nigella sativa*

The plant *Nigella sativa*, also called black seeds, member of Ranunculaceae botanical family and due to its wide range of pharmacological characteristics, historical and religious background it is recognized as a miracle herb. It is mostly cultivated in South Europe, Northern African countries and Southwest Asian countries, Mediterranean region, Syria, Pakistan, India, Turkey and Saudi Arabia [8]. It is an annual flowering plant, 20-30 cm length having linear and leaves are of lanceolate shape. Flowers contain 5-10 petals with variety of colors such as white, yellow, blue, pink. It has fruit that is composed of 3-7 follicles having many black colored, trigonous, oblong, angular seeds which have bitter taste, aromatic smell and dimensions include length 0.2 cm and width 0.1 cm. Both, seed and oil, are famous to be used as traditional medicine whereas *Nigella sativa* has lot of importance in Unani and Ayurvedic traditional and herbal treatment system [9]. The *Nigella sativa* is used for its unique and wide range of biological and therapeutic properties including diuretic, antihypertensive, antidiabetic, immunomodulatory, analgesic, anthelmintic, renal and antioxidant, gastroprotective, anti-inflammatory, bronchodilator, antimicrobial, etc. [10]. Thymoquinone is important phytobioactive chemical compound and responsible for most of therapeutic activities [11].

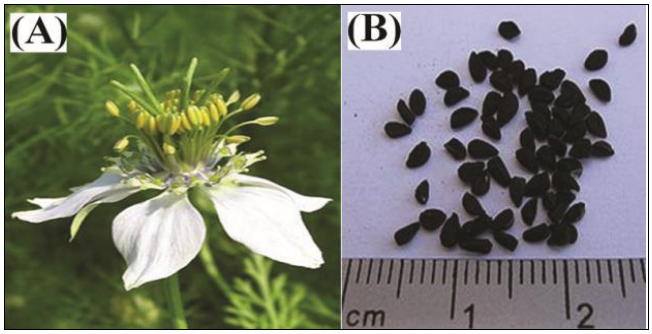

Fig 1: *Nigella sativa* (A) flower (B) seeds

4. Religious importance

The black seeds or black cumin has religious importance as well and according to the Tibb-e-Nabwi (the Prophetic Medicine) it is prescribed to use it regularly to lead a healthy life. In the Islamic scripture of the book of Sahih Al-Bukhari there is a famous hadith by the holy Prophet Muhammad (PBUH) narrated by Hazrat Abu Hurairah (RA), **"**There is cure in the black seeds for every disease excluding death**"** [12].

5. Chemical composition

Nigella sativa contains following proportions of important phytobioactive compounds including the most abundantly found thymoquinone TQ (30%-48%, responsible for majority of the pharmacological activities), whereas the other phytochemicals include dithymoquinone, thymohydroquinone, carvacrol (6%-12%), longifolene (1%-8%), p-cymene (7%-15%), t-anethol (1%-4%), 4-terpineol (2%-7%), α-pinene and thymol, etc. as well as some other important biochemical constituents e.g.limonene, citronellol, carvone, etc. which are mostly present in essential oil and these are responsible for antioxidant potential to ameliorate the oxidative stress [13]. Furthermore insulinotropic characteristics, minimizing the cholesterol level, maintaining the β-cells integrity and neutralizing the untoward effects of drug are also associated with phytobioactive compounds of black cumin [14].

6. Nutritional and phytochemical composition

Nigella sativa is composed of fatty oil (35.6-41.5%), fat (28.5%), protein (26.7%), ash (4.8%), crude fiber (8.4%), carbohydrates (24.9%), and volatile oil (0.5-1.6%), (Ahmad, *et al*., 2013), moisture (8.1-11.6%) and cellulose (6.8-7.4%) [15]. Vitamins and minerals are present in berries in considerable proportions. The vanillic acid is present in roots whereas carotene is present in seeds. The unsaturated fatty acids include dihomolinoleic acid (10%), oleic acid (20%), eicodadienoic acid (3%), and linolic acid (50-60%) whereas main saturated fatty acids include stearic acid and palmiticacid in which stigmasterol (6.57-20.92%) and α-sitosterol (44-54%) are pioneers [16]. In addition to this other fattyacids present in black seeds include palmitoleic acid, linolenic acid, arachidonic acid, linoleic acid, campesterol, Δ5-avenasterol, β-sitosterol, Δ7-stigmasterol, and Δ7-avenasterol [15].

The phytochemical analysis, as reported by [17] shows a diverse group of other phytobioactive compounds i.e. nigellicine, carvone, nigellone, cycloeucalenol, citrostradienol, lophenol, gramisterol, stigmastanol, ostusifoliol, butyrospermol, β-amyrin, tirucallol, taraxerol,

cycloartenol, 3-O-[β-Dxylopyranosyl (1→3)-α-L-arabino-pyranosyl]-28-O-[α-Lrhamnopyranosyl(1→4)-β-D-glucopyranosyl(1→6)-β Dglucopyranosyl] hederagenin, β-unsaturated hydroxyl ketone, esters of dehydrostearic and linoleic acid, melanthigenin, melanthin, resin, 3-O-[β-D-xylopyranosyl (1→2)-α-Lrhamnopyrasyl (1→2)-β-D-glucopyranosyl]-11-methoxy-16, glycosidalsaponin, stigma-5, 22-dien-3-β-D-glucopyranoside, nigellidine-4-O-sulfite, 23-dihydroxy-28-methylolean-12-enoate, cycloart-23-methyl-7, 20, 22-triene-3β, 25-diol, N. mines A1, a2, B1, B2, N. mines A3, a4, A5, and C [16], octahydropyrazino [2, 1-a:5, 4-a'] diisoquinoline, decanylnigelloic acid diglucoside [n-decanyl-3-aldehydic-4-methoxy-5-hydroxy benzoate-5-β-D-glucofuranosyl (2→1)-β-Dglucopyranosyl-(2→1)-β-D-glucopyranoside]] and nigelabdienoyltriglucoside [homo-labd-5, 9(11)-dien-16-onyl-β-D-glucopyranosyl (2→1)-β-D-glucopyranosyl (2→1)-β-D-glucopyranoside] [18].

7. Pharmacological effects

7.1. Antibacterial Effect

A trial was performed in rats where the extracts of *Nigella sativa*, together with streptomycin and gentamicin, showed synergistic effect and successfully minimized the infection by *staphylococcus* spp. In the trial filter paper discs, having extract of black cumin @ 25-400 µg/dis, were used to exhibit antibacterial characteristics and resultantly the concentration of Gram positive bacteria (*Staphylococcus aureus*) was reduced [19].

7.2. Antiviral effects

Nigella sativa extract was reported to increase the T4, T8 helper cells, and also increase the cellular activity by natural killer cell [20]. The mice was experimentally infected with murine cytomegalovirus and in order to treat the black cumin oil was intraperitoneally administered which improved the immune system by increasing the T lymphocytes and INF-γ production [21].

7.3. Antioxidant effects

Herbal supplements' antioxidant characteristic prevent the living bodies against fatal diseases including cancer, cardiovascular and neurodegenerative diseases. A research trial was conducted where the phytobioactive compounds (thymoquinone, carvacrol, tanethole, and 4-terpineol) of black cumin enhanced the antioxidant status and exhibited the scavenging characteristics [22].

7.4. Anti-diabetic Effect

In carbohydrate and lipid metabolism, efficacy of L-carnitine and α-lipoic acid (α-LA), along with black seed, was investigated in rats which were administered streptozotocin @ 65 mg/kg intraperitonelly. The glucose metabolism can be determined by the blood glucose level in fasting situation, insulin, C-peptide, and the activity of pyruvate dehydrogenase enzyme. In this situation α-LA and the black cumin both have potential to minimize the elevated blood glucose level. In diabetic rats, a considerable improvement is seen in the carbohydrate metabolism when the rats were offered mixture of α-LA, L-carnitine and black seeds.

The diabetes was reported to increase concentrations of malondialdehyde MDA, glucose and decrease insulin's proportion and superoxide dismutase. To counter this condition, the aqueous extract and oil of black cumin both were administered and the effects were evaluated on the serum insulin, glucose levels, SOD and MDA level in pancreatic tissues of streptozotocin-induced diabetic rats. It was reported that the treatment successfully minimized the diabetes-induced increase of MDA, and remarkably increased the insulin and superoxide dismutase levels. The thymoquinone was reported to affect at molecular level by neutralizing streptozotocin detrimental effects e.g. heterochromatin material, mitochondrial vacuolization and fragmentation. The results showed that black cumin extract and thymoquinone imparted the anti-diabetic impacts diabetic rats by decreasing the oxidation stress along with maintaining the integrity of pancreatic β-cells [23].

8. Myrtle (*Myrtus communis* Linn)

This plant is a spontaneous, evergreen and an important member of Mirtaceae and subfamily Myrtoideae which contains 145 genera and almost 5500 species and mostly grows in Mediterranean region. The genus of this family is composed of flowering plant having 16 species which are found in Middle East and Asian countries. The rosemary residues, thyme residues and their EO are widely used in the feed of animals [24] but that of myrtle has not been widely reported [25].

Myrtle is an evergreen sclerophyll small tree with minimum length of 1.8-2.4 centimeter [26]. There are thick, ovate or lanceolate green 3.5 cm long leaves which contain important phytochemicals such as tannins, flavonoids and EO [27]. The fruit of myrtle can be of two specific colors - dark or white, and most of the times the fruits are of dark color [28]. The dietary usage of myrtle plant in animals may be useful for extending the shelf life and also for maintaining the meat and carcass quality.

Fig 2: Myrtle leaves and berries

9. Chemical composition

Myrtle plant's leavesare composed of linalool (7.7-15.8%), 1, 8-cineole (13.5-19.6%), terpinolene, linalyl acetate (2.5-6%), flavonoid and tannins [29]. The fruits contain fatty acids organic acids (9-52%) and anthocyanins (0.2-54%) [30]. In myrtle α-pinene (~10-60%) and 1, 8-cineole (~12-34%) compounds are commonly found in stem, flowers and leaves [31].

The essential oils are found in hairs, glands, cavities, resin ducts or ducts [32]. Although the essential oils are important phytochemicals but generally their concentration in total mass of the plant rarely exceeds to 1% [33]. The proportion of EO in stem, flower and leaf is 0.08%, 0.30% and 0.61% respectively [31]. The EO does not have any color, or slight yellow, hydrophobic, non-polar, less dense as compared to water, and soluble in alcohol [34]. The oils are composed of Z-3-hexenol, E-2-hexenal, α-thujene, hexanol, tricyclene, α-pinene, β-pinene, sabinene, α-terpinene, δ-3-carene, myrcene, p-cymene, E-β-ocimene, 1,8-cineole, limonene, terpinolene, E-oxide, borneol, linalool, terpinene-4-ol, p-cymene-8-ol, nerol, α-terpineol, myrtenol, cis-carveol, bornyl acetate, geraniol,

eugenol, myrtenyl acetate, linalyl acetate, geranyl acetate, methyl eugenol, α-terpinyl acetate, β-caryophyllene, neryl acetate, germacrene-D, alloaromadendrene, α-humulene, spathulenol, thiophene, nonadecane, β-elemene, geranyl 2-methylbutyrate, camphene, α-phellandrene, cis-linalool oxide, caryophylleneoxide,tridecane and trans-linalool oxide. Mainly the EO is divided into below mentioned categories [35-36].

- Terpenes (sesquiterpene hydrocarbons and monoterpene hydrocarbons)
- Terpenoids (oxygenated sesquiterpenes and oxygenated monoterpenes)
- Phenylpropanoids

Similarly *Myrtus communis*plant extracts are composed of polyphenols, and these chemical compounds are divided into 3 main categories.

- Phenolic acids include ellagic, garlic, vanillic, ferulic acid and syringic)
- Tannins include condensed tannins (Proanthocyanidins) and hydrolysable tannins (gallotannins)
- Flavonoids include quercetin, myricetin, catechin, and their respective derivatives which include myricetin-3-d-galactoside, myricetin-3-d-rahmnoside, quercetin-3-rutinoside, catechin derivatives (Flavanols) andquercetin-3-d-rahmnoside [31, 37].

10. Pharmacological effects

10.1. Antibacterial effect

In a trial the myrtle crude extracts decreased the growth of *Micrococcus luteus, Staphylococcus aureus, Streptococcus pyogenes, Proteus vulgaris, Streptococcus agalactiae, E. coli, Listeria monocytogenes*, and *Campylobacter jejuni*. Minimum inhibitory concentration (MIC) ranged from 0.1 for *S. aureus* and *M. luteus* to more than 2 mg/ml for *E. coli*. The myrtle extracts exhibited increased MIC of 0.025 mg/ml for *Staphylococcus aureus* and *Micrococcus luteus* and MIC of 0.1 mg/ml for *Escherichia coli*. The myrtle essential oils exhibited resistance activity against *M. tuberculosis* but did not show any activity for *M. avium* [38]. An enhanced antibacterial activity can be exhibited during synergistic effects of essential oils and bacteriophages. The combined impact resulted in damaging the cell wall of bacteria by EO either penetrates the bacteriophage in cells or stimulatory effects of bacteriophage and essential oil on cell membranes [39].

10.2. Virucidal activity

Essential oils also contain an important characteristic of destroying or dismantling the viruses by denaturing the viral glycoproteins [40]. According to [41] there are below mentioned two possibilities of mode of action.

- Inhibition of specific processes in the replication of virus.
- Masking viral components using which the virus adsorbs and penetrates into the host cell.

In addition to the above mentioned possible modes of action, some phytochemicals also function by inhibiting the synthesis of nucleic acid or inhibiting stages in virus's multiplication process [42]. The plants of this family contain an important antiviral compound α-caryophyllene [40].

10.3. Gastrointestinal effects

A research trial was performed by [43] where black seed extract was given to the laparotomized Wistar rats @ 25, 50, and 100 mg/kg, and the findings revealed below mentioned results.

- Healed the esophageal damage.
- Reduced malondialdehyde MDA concentration.
- Potentiated some enzymes e.g. CAT, SOD, etc.
- Increased the plasma scavenging activities.
- Involved in regulating the calcium ions' balance ultimately balancing and restoring the ion homeostasis.

Similarly the Wistar rats were experimentally given ethanol or indomethacin and an aqueous extract of myrtle barriers was given to the rats which reduced the ulcer index, and gastric acidity [44]. In a similar research trial the Wistar rats were experimentally given castor oil and then given myrtle aqueous extract @ 25, 50 and 100 mg/kg which reduced diarrhea, minimized the oxidative stress, and potentiated the antioxidative enzymatic activities [43]. In another trial on the Wistar rats, juice of myrtle barriers was used @ 5 and 10 ml/kg which reduced gastric emptying, gut activity, prevented diarrhea, lowered stress of oxidative process, increased the enzymatic activities, etc. [45].

Table 1: Effects of extract of *Myrtus communis*

Extract	Wistar rat model	Dose rate	Impacts	Reference
Aqueous extract	Laparotomized male	25, 50, and 100 mg/kg for 6 hours	Healing of histopathology Low oxidation stress Enhanced antioxidative enzymatic activity Reinstatement of homeostasis of ions	[43]
Aqueous and methanolic extract of berries	Gastric ulcer induced by ethanol	105 and 175 mg/kg 93 and 154 mg/kg for 1-5 hour	Reduced ulcer, mucus, acidity Healing of the histopathology	[44]
Juice of berry	Diarrhea induced by castor oil	5-10 ml/kg for 1 hour	Lower the chances of diarrhea Lower the oxidation stress Enhanced activity of enzymes	[45]

10.4. Anti-diabetic effects

The phytobioactive compounds are considered very effective in lowering or preventing the risk of diabetes mellitus which is an important disease regarding the human health [46]. In a trial aqueous extract of black cumin was used @ 400 and 800 mg/kg in rats and the results showed significant effects on levels of glucose, urea, serum lipid and creatinine level, and liver enzyme [47]. In another trial the myrtle essential oil was used in alloxan-induced diabetic rabbits and findings of trial revealed significant reduction in glucose level, triglyceride level, hepatic nitrite, and also affected glucokinase and concentration of glycogen whereas the serum insulim level was not affected [48].

The black cumin extract have potency to reduce the chances of diabetes mellitus in streptozotocin-induced diabetic rats whereas the extract didn't show its effects on blood glucose level when used on normal rats. Furthermore EO of myrtle leaves can decrease glucose level in type-2 diabetes and can

induce hypoglycaemic (by enhancing glycolysis, glycogenesis and by decreasing glycogenolysis) and mild hypotriglyceridemic condition in diabetic animals. The myrtle essential oil has the ability to decreases the intestinal glucose uptake as well as inhibit α-glycosidase enzyme which has the potency to induce hypoglycemia in diabetic rabbits [49]. Myrtle leave extract @ 800 mg/kg BW was used on diabetic rats and the results revealed antihyperglycaemic effects, moreover the administration also had significant effects on blood biochemical parameters such as triglycerides, cholesterol, glucose, HDL, LDL, AST, ALT, BUN, total proteins, creatinine, albumin and globulin [50].

10.5. Anti-inflammatory effects

The myrtle plant contained anti-inflammatory activity as it was reported in a research trial where the myrtle plant extracts @ 10 ml/kg was used in rats [51]. Similarly black cumin extract protected the albino mice against xylene-induced inflammatory response [52]. The myrtle seeds @ 25, 50, and 100 mg/kg was used on ethanol intoxicated rats which descended the concentration of IL-8, TNF-*α*, IL-1*β*, IL-6, and lipid peroxidation, etc. [53].

In an in-vivo and in-vitro trial on alloxan induced rats, the decoction of Sahara myrtle was orally administered @ 100 and 300 mg/kg BW, along with Glibenclamide@ 5 mg/kg (reference drug), to check its effects and the results revealed significant antihyperglyceamic effects at high dose rates. It was concluded that the diabetes lowering activity of Sahara myrtle was possibly because of high phenolic, tannin, and flavonoid contents [54].

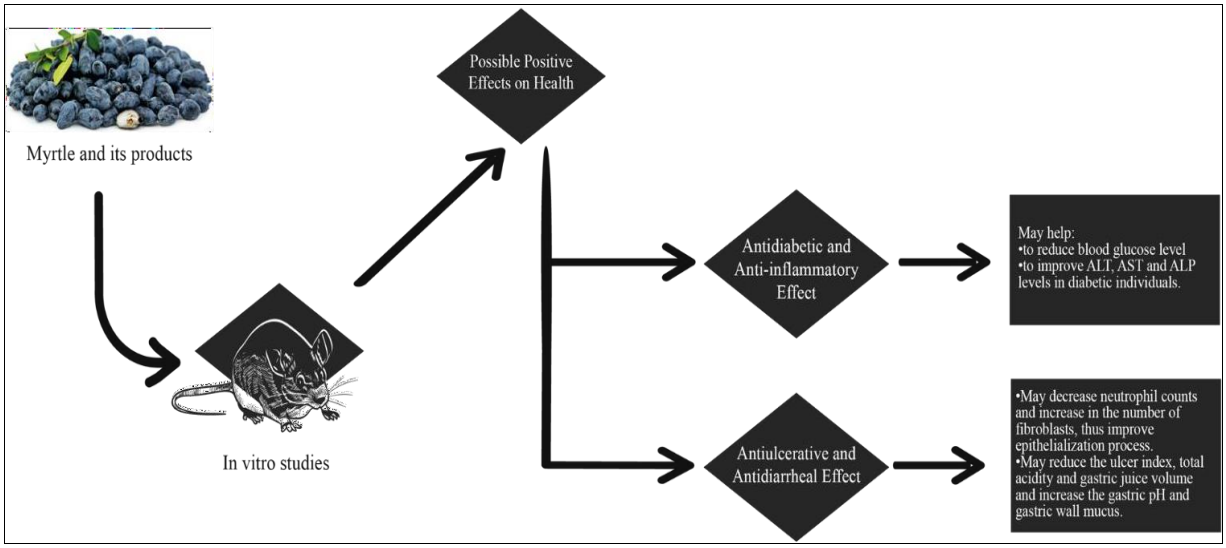

Fig 3: The potential positive effects of myrtle on the health of rat

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