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Fortification of Functional Foods for Human Health: A Case Study of Honey and Yogurt for Diabetes

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Day by day, human faces many diseases that may depend on several factors including the lifestyle and genetic factors. After COVID-19 spreading, several sectors in our life are totally changed particularly the global medical system, which has been pushed to its breaking point. Furthermore, many human diseases, especially for the elderly and those with comorbidities, are at a great risk for adverse outcomes due to COVID-19 such as diabetes mellitus, hypertension severe obesity, and coronary disease. As one of the global top 10 deathly diseases, diabetes mellitus can cause many health complications including cardiovascular disease, chronic kidney disease, stroke, damage to the nerves, eyes and cognitive impairment. Beside the pharmaceutical treatments against diabetes, several functional foods (particularly honey and yogurt) could be fortified with many essential nutrients like copper, iodine, selenium, and zinc. These functions foods are rich in many bioactive ingredients, which support the human body to fight against such diabetes such as phenolic acids, flavonoids, vitamins and antioxidants. Feeding the human with yogurt mixed with the honey, which already has been fortified with many essential nutrients or vitamins, is important a new approach in fortification program again diseases like diabetes. This study opens new windows in the fortification field towards the human fighting against diseases like diabetes.

Keywords: Agronomic fortification, Bioactive ingredients, Nanonutrients, Biofortification, Bioaccessibility, COVID-19.

1. Fortification and its approaches

Humans need certain essential nutrients, which must be involved in the human diets. These nutrients are presenting in soil and then cultivated plants in these soils. The problems resulted from nutrient non-bioavailability in soils for cultivated plants may lead to malnutrition for people who rely on those plants as a source of foods. Therefore, there is a need for the supplying of these nutrients for cultivated plants by fertilization or other methods, which called the biofortification (Table 1; El-Ramady et al. 2021a). The main approached of biofortification may include the agronomic or fertilization, conventional breeding, modern biotechnology, and nano-biofortification (Zheng et al. 2020; El-Ramady et al. 2021b; Olson et al. 2021; Silva et al. 2021). Biofortification has been applied for many edible food crops such as cassava, maize, pear, potato, sweet potato, rice, strawberry, wheat, and pulse crops (El-Ramady et al. 2021c). Concerning the nutrients that have been biofortified, they include boron, calcium, copper, iodine, iron, selenium, and zinc (Saffarionpour and Diosady 2021). Not only the nutrients can apply to edible crops but also the vitamins, which could biofortify like vitamin A, C (ascorbate), E (tocopherol), B1 (thiamine), B3 (niacin), B5 (pantothenate), B2 (riboflavin), B7 (biotin), B6 (pyridoxine), B9 (folates), B12 (cobalamin), and carotenoids (El-Ramady et al. 2021a). The absent or deficit of both nutrients and vitamins cause many healthy problems or diseases for humans as presented in Table 2

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Table 1. A comparison between fortification of foods and biofortification of cultivated crops.

Item of comparison	Fortification of foods	Biofortification of crops
Definition	It is the process of enriching foods with needed nutrients during their processing to increase the healthy and nutritional value [1]	It is a food-based approach or process, by which might increase the bioavailability and/or level of nutrients or vitamins in crops [2]
Main purposes of fortification	1- Overcome micronutrient deficiencies 2- Treatment for diseases (e.g., anemia) 3- Fighting malnutrition [3]	The same three strategies but using cultivated edible plants
Main approaches	1- Conventional fortification 2- Encapsulation and nanoparticulation 3- Mineral-chelate complexes 4- Postharvest processing [4]	- Agronomic biofortification [5] - Conventional breeding [1] - Modern biotechnology [6] - Nano-biofortification [14], [15]
Which fortified foods or crops are targeted?	- Cereals: rice, maize, wheat, sorghum - Legumes: cowpea, sesame, groundnuts - Oil crops: sesame, groundnuts [7] - Vegetable crops: sweet basil, tomato and garlic [8], [9], [10], [11] - Fruit crops: apple and strawberry [12], [13]	The same cereals, legumes, fruits, vegetables
Which materials are preferred for fortification?	Flour, cheese, salt, yogurt, honey, etc. during the industrial processing [21]	Only during the agricultural, growth and production of edible crops
Main fortification vehicles	The applying of micronutrients during post-harvest processing of consumed foods with salt, flours, sugar, oil, and condiments [16]	Biofortified crops by adding nutrients, fertilizers, amino acids and others during grow food crops are grown to improve their nutritional value [16]
Main fortificants	Vitamins: A, B_1, B_{12}, C, D, E, and K Nutrients: Ca, F, I, Mg, Fe, Cu, Se, Zn Substances: folate, carotenoids, essential oils, omega-3, and antioxidants [17]	The same for cultivated edible plants
Main limitations	Impracticality, instability, and high costs of some added materials during postharvest [18]	Are biofortification practices implement effectively global agro-economy under COVID-19? [19]
Main policy guidance and regulations	Evaluating, implementation, monitoring food quality, and food safety as well as acceptability, storage stability, and appearance [4], [20]	No limitations for biofortification for all nutrients globally are established or still not consider a global strategy for fighting the malnutrition [14]

List of refs. (1) Olson et al. (2021); (2) Tiozon et al. (2021); (3) Bhargava et al. (2021); (4) Saha and Roy (2020); (5) Silva et al. (2021); (6) Zheng et al. (2020); (7) Desire et al. (2021); (8) Buturi et al. (2021); (9) Sabatino et al. (2021); (10) Puccinelli et al. (2021); (11) Sohrabi et al. (2020); (12) Budke et al. (2021); (13) Budke et al. (2020); (14) El-Ramady et al. (2021b); (15) El-Ramady et al. (2021c); (16) Olson et al. (2021); (17) Saffarionpour and Diosady (2021); (18) Mattar et al. (2022); (19) El-Ramady et al. (2021a); (20) Saha et al. (2021), and (21) Kennas et al. (2020).

Table 2. List of minerals and vitamins from human nutrition and their required concentrations.

Nutrients or vitamins	Main and common function	Recommended dietary allowance (RDA) per day		Absorption rate (%) (common disease related to deficiency)
		Men	Women	
Vitamin A	Vision, immune function	900 µg	700 µg	90 (Night Blindness)
D	Bone health	600-800 IU	600-800 IU	50 (Osteoporosis)
E	Antioxidant	15 mg	15 mg	20-50 (nerve problem)
K	Bone metabolism	120 µg	90 µg	20-80 (Hemophilia)
B1 (thiamin)	Nerve function	1.2 mg	1.1 mg	------- (Beriberi)
B2 (riboflavin)	Convert B6 to be active	1.3 mg	1.1 mg	95 (stomatitis)
B3 (niacin)	Carbohydrate metabolism	16 mg	14 mg	------ (Pellagra)
B6 (pyridoxine)	Hemoglobin synthesis	1.7 mg	1.5 mg	75 (somnolence)
B12 (cobalamin)	Convert folate to be active	2.4 µg	2.4 µg	50 (anemia)
B_9 (folates)	Red blood cell synthesis	400 µg	400 µg	50-100 (megaloblasts)
C (ascorbic acid)	Neurotransmitter synthesis	90 mg	75 mg	80-90 (Scurvy)
Calcium (Ca)	Component of bones, teeth	1.0–1.2 g	1200 mg	15-60 (Rickets)
Chloride (Cl)	Nerve-impulse transmission	2.0 g	1.8 g	------------
Copper (Cu)	Red blood cell formation	900 µg	900 µg	20-60 (hypocupremia)
Iodine (I)	Thyroid hormone synthesis	150 µg	150 µg	------ (Goiter)
Iron (Fe)	Formation of hemoglobin	8 mg	8 mg	10-30 (anemia)
Magnesium (Mg)	Cardiovascular excitability	420 mg	320 mg	30-40 (nystagmus)
Manganese (Mn)	Metalloenzymes component	2.3 mg	1.8 mg	1-5
Molybdenum, Mo	Enzyme component	45 µg	45 µg	85-93
Phosphorus (P)	Muscle and nerve function	700 mg	700 mg	60-70
Potassium (K)	Protein, glycogen synthesis	4.7 g	4.7 g	------ (Hypokalemia)
Selenium (Se)	Thyroid function	55 µg	55 µg	50-100 (Keshan)
Sodium (Na)	Regulate water distribution	1.3 g	1.2 g	----- (Hyponatremia)
Zinc (Zn)	Growth of genital organs	11 mg	11 mg	20-40, grow retardation

Sources: Doley (2017), Wikipedia (https://en.wikipedia.org/wiki/List_of_types_of_malnutrition) and Curko-Cofek B (2021).

2. Functional foods and their potential

Functional foods are foods that contain one or more ingredients, which have a positive effect on human health. These foods also have more functionality than normal because one or more ingredients are less than normal foods in the same category or some substances are concentrated. The effects can involve suppression of oxidative damage and microbial infections (Calder and Kew 2002; Taira, 2021), dietary fiber activity, immunostimulatory effects (Ashaolu, 2020), nervous system stimulatory effects (Magrone et al. 2013), estrogenic effects (Markovic et al., 2015; Domínguez-López et al., 2020), antiallergenic effects (Ouwehand, 2007), and cholesterol-lowering (Sutton et al., 2009; Baumgartner et al., 2020) and antihypertensive effects (Saleh et al., 2016; Venkatakrishnan et al., 2020). Generally, functional foods are including conventional and modified foods. Conventional foods are all-natural food ingredients rich in important nutrients such as vitamins, minerals, antioxidants and fats that are good for heart health, which is including fruits, vegetables, nuts, seeds, legumes, whole grains, seafood, meats, fermented foods, herbs and spices, and some beverages (Alongi and Anese 2021). Modified foods are fortified with additional ingredients such as vitamins, minerals, probiotics and fiber to enhance the health benefits of the food, is providing fortified juices, fortified dairy products, fortified milk alternatives, fortified grains, fortified cereal and granola, fortified eggs, etc. The health-promoting properties of these foods are due to bioactive ingredients such as polyphenols, flavonoids, sulforaphane, isothiocyanates, peptides, stanols or sterols, carotenoids, fibers, probiotic bacteria, essential fatty acids, etc.

Functional foods rich in antioxidants such as plant polyphenols, flavonoids, vitamins C and E, carotenoids or vitamin A, and minerals like selenium and zinc, can inhibit LDL oxidation, alter the activity of immunocompetent cells, and inhibit the formation of intercellular adhesion factors, thus providing potential cardiovascular protection. These extrinsic antioxidants may be involved in the regulation of mitochondrial reactive oxygen species (ROS). They can be found in fruit juices, coffee, tea, red wine, onions, apples and berries, black currants, blueberries, honey, Brazil nuts, and fortified functional foods, etc. For example; the hydroxyl groups of polyphenols attached to the phenolic ring make them an excellent antioxidant. The flavonoids such as catechin, catechin gallates, quercetin, kaempferol, etc. can alter the activity of major enzymes and have vasodilatory (Abdallah et al., 2020; Monori-Kiss et al., 2014), anticancer (Kopustinskiene et al., 2020), anti-inflammatory (Maleki et al., 2019), and immune-potentiating effects (Gricelis et al., 2019).

Functional foods rich in essential fatty acids including omega-3 (ω-3) and omega-6 (ω-6) can have beneficial effects on heart health (Defilippis et al., 2010; Dimri et al., 2010) and other medical conditions such as cancer (Dimri et al., 2010), psoriasis (Zulfakar et al., 2007), bowel disease (Diamond et al., 2008) and neurological disease (Bousquet et al., 2008; Eckert et al., 2010). They can be found in fish, fish oils, some vegetable oils, safflower, sunflower, corn, soybean, sesame, almond, black currant, borage, meat, eggs, and dairy products. Omega-3 fatty acids like alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) improve energy levels, reduce cardiovascular risk factors and inflammation, suppress cancer growth and metastasis, increase insulin sensitivity, accelerate accidental injury, reduce joint pain and weakens autoimmune symptoms, improve bone mineral metabolism, improve weight management, and increase fat burning and decrease fat production.

Functional foods rich in probiotics, mainly containing lactic acid bacteria belonging to the genus Lactobacillus and Bifidobacterium. They can normalize the gut microbiota, treat some types of diarrhoeas, reduce the symptoms of irritable bowel syndrome or inflammatory bowel disease, improve lactose intolerance, prevent colon cancer, and regulate immune function. They also can enhance calcium absorption, reduce blood cholesterol, inhibit potential intestinal pathogens and Helicobacter pylori. Probiotics can be found in both conventional and modified functional dairy foods such as yoghurt, cheese, milk, kefir, and some fermented foods like kimchi, sauerkraut, tempeh, kombucha, fermented mare’s milk, etc. For example; probiotic strains like *L. rhamnosus*, *L. casei*, *B. bifidum* and *S. thermophilus* have effectively treated rotavirus diarrhoea (Ahmadi et al., 2015; Kawahara et al., 2017; Pant et al., 2007). *Lactobacillus* strains such as *L. rhamnosus*, *L. helveticus* and *L. casei* have induced early proinflammatory cytokines and phagocytosis and bactericidal activity of macrophages (Rocha-

Ramírez et al., 2017). The consumption of milk or yoghurt containing *Bifidobacterium* strains such *B. lactis* and *B. longum* leads to a significant reduction in triglyceride, low-density lipid, and total cholesterol (Xiao et al., 2003; Abd El-Gawad et al., 2005).

In general, there are several topics to be discussed about functional foods for manufacturers and consumers. For instance; which ingredients should be added to the food, or which ingredients should be found in it? What are the specific ingredients that can make a food work in a higher proportion? What is the safest dose? What are the benefits of administering this ingredient? What will the product be and what can we manufacture?

Table 3: Main information about diabetes disease and its phyto-treatments

Item	More details concerning the items	Reference
Diabetes mellitus definition	It is a metabolic disease in which the body is not able to produce the hormone insulin that resulted from abnormal carbohydrates metabolism and elevated glucose levels in the blood	Shabab et al. (2021)
Types of diabetes mellitus	1- Type 1 diabetes mellitus 2- Type 2 diabetes mellitus 3- Gestational diabetes mellitus	Sharma et al. (2022)
Main risks or complications	- Diabesity and brain damage - Atherosclerosis - Cardiovascular or cerebrovascular disease - Kidney failure and eye complications - Hypertension, lipoprotein abnormalities - Reproductive system	Sharma et al. (2022)
Main treatments for diabetes		Tripathy et al. (2021)
- Drug treatments	Sulfonylureas, metformin, alpha glucosidase inhibitors, SGLT2 inhibitors, thiazolidine-diones, DPP-4 inhibitors, GLP- 1agonists, amylin analogues	Sharma et al. (2022)
- Phyto-treatments	**Polyphenols:** catechins, luteolin, quercetin, genistein, resveratrol	Sharma et al. (2022)
	Phenols: chebulagic acid, corilagin, repandusinic acid A, mallotinin, lagerstroemin, flosin B, reginin A, curcumin	Andrade et al. (2020)
	Alkaloids: vindogentianine, vindolicine vindoline, mitragynine, aegeline	Andrade et al. (2020)
	Terpenoids: geraniol, orthosiphol A, costunolide, eremanthin, borapetoside A, B, C, D, E, andrographolide	Andrade et al. (2020)
Main symptoms of diabetes	Increased thirst, blurred vision, weak, tired feeling, tingling or numbness in the hands or feet, frequent urination, low-healing sores or cuts, unplanned weight loss, dry mouth	Alam et al. (2021)
Common and high level of diabetes		Alam et al. (2021)
- Normal cases	Less than 5.6 mmol/L (fasting glucose test) Less than 7.0 mmol/L (random glucose test)	
- Diabetes cases	7.8 or higher mmol/L (fasting glucose test) 11.1 or higher mmol/L (random glucose test)	

3. Diabetes as deathly disease

World Health Organization (WHO) reported that, the top 10 diseases cause human death accounted for 55% of the 55.4 million deaths worldwide in 2019. The list of these diseases includes ischaemic heart disease (16%), stroke (11%), chronic obstructive pulmonary disease (6%), lower respiratory infections (2.6 million), neonatal conditions (2.0 million), trachea, bronchus and lung cancers (1.8 million), Alzheimer's disease (1.6 million), diarrhoeal diseases (1.5 million), diabetes mellitus (1.4 million), and kidney diseases (1.3 million) (WHO 2021). Diabetes is considered a great challenge facing the globe in 21st century (**Table 3**), which results from metabolic disorder in carbohydrates that increase glucose level (hyper-glycemia) because of insufficient insulin secretion and /or action or both (Sharma et al. 2022). This disease causes multi-organ failure including heart diseases and stroke, hepatorenal damage, nerve damage, adult-onset blindness, high blood pressure, and lower-limb amputations. Furthermore, diabetic patients may have higher risks of cardiovascular complications including lipoprotein abnormalities, atherosclerosis, hypertension, and cerebrovascular diseases (Sharma et al. 2022). The global diabetes prevalence was estimated to be 463 million people in 2019 and will increase to be 578 million by 2030 and 700 million by 2045 (Tripathy et al. 2021). The main problem of this disease that diabetes has high and increasing rate in every country, which is fueled by the global rise in the prevalence of obesity and unhealthy lifestyles as well (Alam et al. 2021). The top 10 territories or countries are identified for the highest number of people with diabetes in 2019 include China (116 million), India (77 million), the United States of America (31 million), Pakistan (19 million), Brazil (16 million), and Mexico (12 million), as reported by Alam et al. (2021).

Table 4. The main information about honey including pharmacology and clinical uses.

Item	More details concerning the items	Reference
Honey from different languages	Honey is the name in English, asl (Arabic), Édesem (Hungarian), der Honig (German), le Miel (French), and miele (Italian)	
Honey definition	Honey is a nutritious thick carbohydrate-rich natural syrup, viscous liquid with a delectable taste, and one of the best-known functional foods	Nezhad-Mokhtari et al. (2021); Nikhat and Fazil (2022)
Main types of honey	About 300: acacia, alfalfa, almond, citrus, avocado, clover, coffee, coriander, mad, honeydew honey, Manuka, rosemary, Sahara honey, Sidr Honey, and sunflower honey	HYS (2021)
Honey against main diseases	Anti-allergy, anti-Alzheimer, anti-bacterial infections, anti-cancer, anti-cardiovascular diseases, anti-diabetes, anti-obesity, anti-sexual dysfunctions, thyroid conditions	HYS (2021)
Bioactive ingredients	Phenolic acids, flavonoids, organic acids, minerals, enzymes, proteins, and vitamins	Nezhad-Mokhtari et al. (2021)
Bioactive compounds	Promising health effects like anti-diabetic, anticancer, antioxidant, etc.	Nikhat and Fazil (2022)
Healing treatments	High contents of methionine, arginine, and proline for collagen creation and fibroblast deposition	Nezhad-Mokhtari et al. (2021)
Natural properties and components of honey		
- Color of honey	Amber or yellow-colored, greenish, grayish reddish (chestnut), bright yellowish (sunflower)	Nikhat and Fazil (2022)
- Acidity (pH) of honey	2.4–4.7	Khan et al. (2018)
- Moisture content	13 – 20 % (17.1 %)	Varga et al. (2020)
- Viscosity	9.9 Pa* s (at 18.9% moisture and 24°C)	Khan et al. (2018)
- Carbohydrates	About 95% of the dry weight of honey	Khan et al. (2017)
- Vitamins, minerals, enzymes	0.5 – 2.1%	Hossen et al. (2017)
Main chemical components of honey		
- Phenolic acids and flavonoids	Caffeic acid, chrysin, chlorogenic acid	Nikhat and Fazil (2022)
- Proteins and enzymes	Leucine, glutamic acid	
- Carbohydrates	Fructose, inulobiose, maltose and sucrose	
- Volatile organic components	Heptanal, hexanal and terpenes	
Main pharmacological and clinical applications of honey		
	Wound healing activity and skin-care Topical anti-microbial and anti-microbial activity Immunomodulatory and anti-diabetic activity Anti-cancer and cardio-protective activity Hepato- and Nephroprotective activity Respiratory diseases and gastrointestinal system Oral health, and anti-aging activity Neuro-protective and anti-atherosclerotic activity Psychological disorders	Nezhad-Mokhtari et al. (2021) Nikhat and Fazil (2022)

4. Honey and yogurt for diabetes

There are many foods that are considered functional foods and very important for human health like honey and yogurt. Honey is natural organic substance produced by honeybees (*Apis mellifera* L.) from the nectar of flowers. Honey also is considered a natural food used as nutritious sweetener and one of the most commonly consumed foods throughout worldwide (Yan et al. 2022). Therefore, the global production of honey in 2019 was 1.9 million ton, which the highest production belongs China (444,100 ton) as 24% of the world total production, followed by Turkey (109,330 ton), Canada (80,345 ton), Argentina (78,927 ton), Iran (75,463 ton), and the USA (71,179 ton) as reported by FAOSTAT (2021). Honey has several valuable bioactive ingredients including phenolic acids (caffeic acid, chrysin), flavonoids, minerals, enzymes, organic acids (lactic acid, glutamic acid), proteins (amino acids), volatile organic compounds (heptanal and hexanal) and vitamins (Nezhad-Mokhtari et al. 2021; **Table 4**). Concerning the applications of honey human health, it has been applied for treatment against pilonidal sinus, burns, non-healing and infected ulcers or wounds, venous and diabetic foot boils. Honey also has several beneficial therapeutic issues for wound healing because of its action as antibacterial, immunomodulatory, which promote wound healing properties (Nikhat and Fazil 2022). Several human diseases could be treated by honey like fighting against COVID-19 (Hossain et al. 2020), diabetes (Meo et al .2017; Bobiş et al. 2018; Sadeghi et al. 2019; Hemadri Reddy et al. 2020; Zamanian and Azizi-Soleiman 2020; Kaya and Yıldırım 2021), or antibacterial activity (Majtana et al. 2021). When honeybees collect their nectar from poisonous plants (e.g., *Rhododendron* sp., *Coriaria arborea*, and *Tripterygium wilfordii* Hook F.), such honey contains natural plant toxins like triptolides, grayanotoxins, tutin and pyrrolizidine alkaloids producing a toxic honey (Yan et al. 2022).

Yogurt also is very important food for human health as a functional food. Yogurt already confirmed its potential against several human diseases like gestational diabetes (Roustazadeh et al. 2021), chronic diseases (Dumas et al. 2017), metabolic syndrome risk factors like hyper-glycemia (Khorraminezhad and Rudkowska 2021). A little published article concerning the using of honey and yogurt against diabetes like Abdelmonem et al. (2012), whose studied the impact of honey-yogurt mixture for treating patients with vulvovaginal candidiasis during pregnancy. Can healthy lifestyle reduce disease progression of several diseases like Alzheimer's (John et al. 2021) or diabetes (Amataiti et al. 2021) or others during a global pandemic of COVID-19. Ramadan fasting for 30 days is one of the most common behaviors, which may has distinguished impacts on diabetic patients (Nassar et al. 2021; Tootee and Larijan 2021).

Therefore, this is a call for submitting articles to publish by EBSS journal about the fortification of functional foods for human health with focus on honey and yogurt against diabetes. This work also is a call for more concerns about the mixture of honey and yogurt, which could be used in human feeding with great chance to fortify this mixture with any necessary nutrients for human health like iodine, selenium, iron, zinc, copper, and other nutrients. Several questions are needed to be answered in this concern like which concentration should we use to fortify this mixture? And which nutrients could be added? Which amount of honey should be added to the yogurt? Which type of honey is suitable to mix with yogurt especially under diabetes problems?

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