Pharmacological Research 187 (2023) 106599

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Bioactive compounds in childhood obesity and associated metabolic complications: Current evidence, controversies and perspectives

Giulia Fiore [a], Martina Chiara Pascuzzi [a], Elisabetta Di Profio [a], Antonio Corsello [a], Marta Agostinelli [a], Alice La Mendola [a], Chiara Milanta [a], Cristina Campoy [b,c,d,e], Valeria Calcaterra [a,f], Gianvincenzo Zuccotti [a,g,h], Elvira Verduci [a,i,*]

[a] Department of Paediatrics, Vittore Buzzi Children's Hospital, University of Milan, Italy
[b] Department of Paediatrics, School of Medicine, University of Granada, Granada, Spain
[c] EURISTIKOS Excellence Centre for Paediatric Research, Biomedical Research Centre, University of Granada, Granada, Spain
[d] Spanish Network of Biomedical Research in Epidemiology and Public Health (CIBERESP), Granada's node, Institute of Health Carlos III, 28029 Madrid, Spain
[e] Instituto de Investigación Biosanitaria de Granada (ibs.GRANADA), San Cecilio University Hospital. Health Sciences Technological Park, 18016 Granada, Spain
[f] Pediatric and Adolescent Unit, Department of Internal Medicine, University of Pavia, 27100 Pavia, Italy
[g] Department of Biomedical and Clinical Sciences L. Sacco, University of Milan, 20144 Milan, Italy
[h] Pediatric Clinical Research Center, Fondazione Romeo ed Enrica Invernizzi, University of Milan, Milan, Italy
[i] Department of Health Sciences, University of Milan, Milan, Italy

ARTICLE INFO

Keywords:
Bioactive compounds
Pediatric obesity
Overweight children treatment
Metabolic syndrome
Biotics
Polyphenols

ABSTRACT

Obesity represents the most frequent chronic disease among children worldwide, with a significant global burden on society. Metabolically unhealthy obesity (MUO) can affect children since their first years of life, and novel therapeutic strategies to tackle metabolic complications are under investigation. This review focuses on bioactive compounds and their possible beneficial effects on obesity, particularly omega-3, docosahexaenoic acid, vitamin D, biotics, polysaccharide macromolecules, polyphenols, inositols, alpha lipoic acid, and bromelaine. Our aim is to summarize current evidence about bioactive compounds in the treatment of obesity, highlighting recent findings on their use in children and adolescents. Most studied molecules are omega-3 and vitamin D, despite the heterogeneity between the studies. Moreover, given the emerging interest in the gut-brain axis in the link between metabolic health and microbiota, various studies on prebiotics, probiotics, synbiotics, postbiotics and polysaccharide macromolecules have been considered. Some preclinical studies seem to highlight a possible role of the polyphenols, even if their clinical evidence is still discussed. Lastly, we describe possible effects of inositols and alpha-lipoic acid. Despite some dietary supplements seem to be promising in overweight subjects, only in a few of them a dose/response efficacy has been found in the pediatric age. Innovative, well-designed and targeted clinical trials are then needed to prove the beneficial effects of these compounds that could support the standard behavioral therapy for obesity.

1. Introduction

1.1. Childhood obesity and metabolically unhealthy obesity: an emerging health issue

Obesity affects an increasing portion of children worldwide: "globesity" is a new neologism that clearly synthetizes this high-prevalence risk globally. UNICEF and World Health Organization (WHO) estimates found that in 2020 overweight and obesity involved 4.4 million children under 5 years of age, the 7.9% of this age group [1]. These numbers increase in the 5–9 years-old range, with one in eight children (11.6%) being with obese and nearly one in three (29.5%) being overweight [2]. Obesity is the most prevalent chronic disease among children worldwide and it is a global significant burden for society [3]. Obesity is associated with a reduced life expectancy and a greater risk for chronic diseases such as insulin resistance (IR) and type 2

* Corresponding author at: Department of Paediatrics, Vittore Buzzi Children's Hospital, University of Milan, Italy.
E-mail addresses: giulia.fiore@unimi.it (G. Fiore), martina.pascuzzi@unimi.it (M.C. Pascuzzi), elisabetta.diprofio@unimi.it (E. Di Profio), antonio.corsello@unimi.it (A. Corsello), marta.agostinelli@unimi.it (M. Agostinelli), alice.lamendola@unimi.it (A. La Mendola), chiara.milanta@unimi.it (C. Milanta), ccampoy@ugr.es (C. Campoy), valeria.calcaterra@unipv.it (V. Calcaterra), gianvincenzo.zuccotti@unimi.it (G. Zuccotti), elvira.verduci@unimi.it (E. Verduci).

https://doi.org/10.1016/j.phrs.2022.106599
Received 28 October 2022; Received in revised form 30 November 2022; Accepted 1 December 2022
Available online 9 December 2022

diabetes (T2D) [4], dyslipidemia[5], steatosis, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea, asthma, polycystic ovary syndrome (PCOS) [6], and mental disorders [7].

Although the concepts of "metabolically healthy obesity" (MHO) and "metabolically unhealthy obesity" (MUO) are common in literature, their definition varies among studies. Only in 2018 Damanhoury, S. et al. proposed the first definition of MHO such as obesity (according to WHO criteria) without any metabolic disorder and with a "favorable" metabolic profile (normal glucose regulation, blood pressure and lipids profile) [8–10]. On the contrary, MUO is characterized by metabolic complications such as hyperinsulinemia, IR, arterial hypertension and dyslipidemia [11]. During the last years clinical research has outlined the underlying factors leading to the development of metabolic disturbances in pediatric obesity, mainly attributed to an insulin resistance subsequent to the adipose tissue inflammation (Fig. 1) [12,13]. In pubertal age a physiological decrease in insulin sensitivity occurs, with a subsequent transition from the MHO phenotype to the MUO one [10,14,15]. Metabolic complications occur earlier in children and adolescents suffering from severe obesity, worsening as the obesity severity increases.

Even if there is no standard definition for MHO, particularly in pediatrics, patients with MHO should not be misinterpreted as a subgroup of people with obesity without any health disorder, and it cannot be considered as a benign condition, due to its increased risk of worsening.

In the presence of obesity with metabolic alterations, the definition of metabolic syndrome (Mets) has thus been proposed. Regarding pediatric population, it is not available an universally accepted definition of Mets, but different delineations have been proposed during the years [16–18]. A correct and precise definition of pediatric Mets is of key importance since few studies described an increasing incidence of pediatric Mets, and suggested the presence of a syndrome track from childhood to adulthood, increasing risk especially of type 2 diabetes and atherosclerotic cardiovascular diseases [19,20]. Table 1 sums up the recent proposal by Damanhoury and colleagues of a harmonized definition of MHO in pediatric age, comparing it with the analogue criteria used for the definition of metabolic syndrome [8,17,18].

Table 1
A comparison of MHO and metabolic syndrome criteria among pediatric age.

Metabolically Healthy Obesity (2–18 years) [8]	Metabolic Syndrome Criteria 2–10 years IDEFICS-monitoring level [17] values of at least three of the components of Mets exceeding the 90th percentile:	Metabolic Syndrome Criteria 10–16 years IDF consensus[18]
Obesity according to WHO criteria: > +3 SD weight for height WHO Growth Standards median if younger than 5 years old > +2 SD BMI for age WHO Growth Reference median if older than 5 years old	Waist Circumference ≥ 90°percentile[21]	Waist Circumference ≥ 90°percentile and 2 of the following:
Triglycerides ≤ 150 mg/dl	Triglycerides ≥ 90°percentile or HDL < 10°percentile[22]	Triglycerides ≥ 150 mg/dl or HDL < 40 mg/dl
HDL > 40 mg/dl		
Systolic and diastolic blood pressure ≤ 90th percentile for age	Systolic Blood Pressure ≥ 90° percentile or Diastolic Blood Pressure ≥ 90° percentile[23]	Systolic Blood Pressure ≥ 130 mmHg or Diastolic Blood Pressure ≥ mmHg
A measure of glycemia (most used is fasting blood glucose ≤ 100 mg/dl)	HOMA-index of insulin resistance ≥ 90° percentile or Fasting Plasma Glucose ≥ 90° percentile[24]	Fasting plasma glucose ≥ 100 mg/dl or previously diagnosed type 2 diabetes

Abbreviations: World Health Organization (WHO); Standard Deviation (SD); Body Mass Index (BMI); High-Density Lipoprotein Cholesterol (HDL); Homeostatic Model Assessment index (HOMA-index).

1.2. *Choices for care: behavioral intervention, drugs and bioactive compounds*

The first line of treatment for obesity consists of a multidisciplinary intervention based on dietary counseling, physical activity and behavioral change, with the goal of reducing the caloric intake and increasing

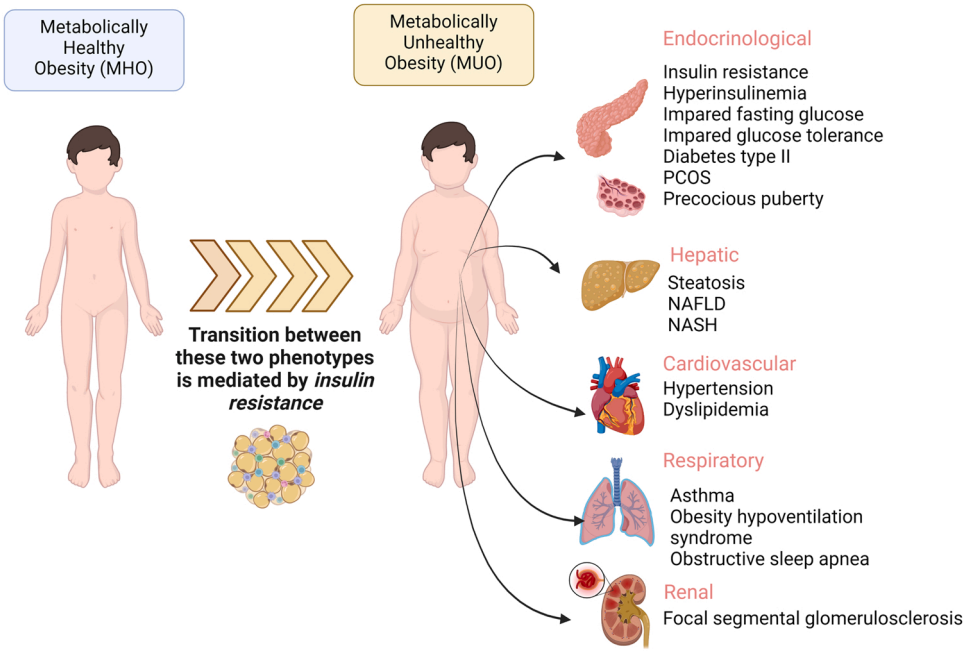

Fig. 1. Metabolically Unhealthy Obesity (MUO) and systemic consequences. Abbreviations: *Polycystic ovary syndrome (PCOS); Nonalcoholic fatty liver disease (NAFLD); Non-alcoholic steatohepatitis (NASH).*

the energy expenditure [25,26]. To improve the adherence to this intervention, motivational interviews and cognitive behavioral therapy (CBT), which involve an assessment of the individual patient's readiness, diet, and physical activity have been found useful in developing a personalized treatment plan for the child and the adolescent [27,28].

The Endocrine Society Clinical Practice Guidelines recommend a minimum of 20 min of physical activity per day, regardless of the amount of adipose tissue, to achieve weight loss, to improve insulin sensitivity and to counteract insulin resistance secondary to obesity [29–31]. Indeed, a 5-, 7- or 10-weeks program of moderate intensity exercise has been shown to promote improvement in various cardiometabolic outcomes, including blood pressure, fat mass, and serum triglycerides in children aged from 5 years old to adolescence, regardless of their weight [32].

Guidelines for good and healthy diet, recommended by the American Academy of Pediatrics (AAP), the American Heart Association (AHA), and the World Health Organization (WHO), call for increased consumption of vegetable and fruit, reduced intake of saturated fats and increased intake of unsaturated ones (e.g., olive oil and other vegetable oils), as well as a reduction in sugar intake [33].

Prescription of weight loss drugs could be useful in the therapeutic management of metabolic syndrome, in selected patients. To date, Orlistat, which acts as an inhibitor of intestinal lipase, and Phentermine, a sympathomimetic amine, are the only weight loss medications approved by the FDA in teenagers aged >12 and >16 years, respectively. Moreover, Liraglutide, a glucagon-like peptide-1 receptor (GLP-1) agonist, has been approved by the FDA in pediatric age (7–11 years) and by the European Medicines Agency (EMA) for 12–17 old children [34].

By the way the first drug of choice in pediatric patients with insulin resistance is the off-label use of Metformin, a biguanide, which can reduce glucose levels by inhibiting the process of hepatic gluconeogenesis promote intestinal glucose absorption [35,36], and increase the concentration in the intestinal lumen of GLP-1 by inhibiting macrophage infiltration in adipose tissue and liver [37].

In the management of dyslipidemia, statins and HMG-CoA reductase inhibitors are recommended as first-line therapy in pediatric patients [38]. However, the AAP recommends their prescription only when lifestyle modifications have failed. According to the National Heart Lung and Blood Institute (NHLBI), children younger than 10 years old should not be treated pharmacologically, unless they have severe primary hyperlipidemia, or a high-risk factor associated with a serious illness. It is also necessary to start a drug treatment in children older than 10 years if LDL cholesterol levels consistently exceed 190 mg/dL, after a 6-month lifestyle intervention attempt [39,40].

Beside the standard treatment for childhood obesity, novel therapeutic strategies are under investigation. Recent findings suggest a possible beneficial role of various bioactive compounds. A bioactive compound is defined as an element or a chemical contained in small amounts in food or food supplements which provides health benefits beyond its theorical nutritional value [41]. The growing interest results from the fact that, being responsible for changes in health status, they have proven useful in the treatment of various diseases [41]. In particular, recent evidence has proposed some bioactive compounds as a possible therapeutic approach for obesity and metabolic syndrome in children and adolescents. In this review we aim to elucidate the current evidence and controversies about the efficacy of bioactive compounds as adjuvant therapies for the management and treatment of childhood obesity.

2. Methods

This narrative review was performed by a comprehensive search of the literature using the following electronic databases: Pubmed/Medline, Embase and Web of Science. The authors independently identified the most relevant studies on the topic. We included original papers, randomized and non-randomized clinical trials, cohort studies, case-control studies and meta-analysis. Case series, literature reviews and other type of publication were excluded. Only articles on pediatric age group (2–18 years) were selected for the final review, while literature on adult population was used to expand the discussion on bioactive compounds. Preclinical studies were considered only to complement descriptions of bioactive compounds mechanisms of action, thereby unifying the molecular basis with the randomized controlled trials (RCT) evidence. We selected papers published over the past 20 years, up to June 2022, by means of the following keywords (alone or in combination): pediatric obesity, children, adolescents, metabolically healthy obesity, metabolically unhealthy obesity, metabolic syndrome, PCOS, nutritional intervention, weight loss, bioactive compound, dietary supplement, omega-3, docosahexaenoic acid, vitamin D, polyphenols, chlorogenic acid, quercetin, phlorizin, curcumin, berberine, bromelain, inositols, D-chiro-inositol, myo-inositol, alpha lipoic acid, polysaccharide macromolecules, prebiotic, probiotic, synbiotic and postbiotic. The selected dietary supplements were identified also in regard of our preliminary work [42]. There are 25 articles on the pediatric population included in the final review, with the following study designs: 1 retrospective study, 2 clinical trials, 18 RCTs, and 4 meta-analysis (Table 2).

3. Bioactive compounds for MUO

3.1. Polysaccharide Macromolecules

Gut microbiota has been found as an important player in human health homeostasis, as it is related with different metabolic pathways. Alterations in its composition, usually defined as "gut microbiota dysbiosis", may negatively affect the well-functioning of human's metabolism [43–45]. Studies on the associations between gut dysbiosis and metabolically healthy and unhealthy obesity have been carried out in both adults and children [46–54]. Changes in the gut microbiota and its derived metabolic products (mainly short-chain fatty acids, SCFAs) could affect feeding behavior and satiety, as well as improve glucose metabolism and dyslipidemia [55,56]. Modulation of the gut microbial community might serve as a basis for new therapeutic strategies in combating metabolic comorbidities associated with obesity and metabolic syndrome [57]. These positive effects on the microbiota are obtained by consuming a diet rich in fibers, which are indigestible to the host and are fermented by the gut microbiota [56,58]. Fibers are non-digestible carbohydrates classified into soluble fibers, responsible for an increase in fecal viscosity, a reduction in glycemic response and a decrease in plasma cholesterol of individuals, and insoluble fibers, characterized by porosity and low density, are associated with increase in fecal bulk and decrease in intestinal transit [59,60]. Dietary fibers include disaccharides, oligosaccharides (FOS, GOS, SBOS) and polysaccharides (inulin, cellulose, hemicellulose, pectin, reflux starch) [60]. Several functions are described: dietary fiber modulates satiety in pre- and post-absorbing phase, decelerates the gastric emptying rate and the stimulus to the production of hormones which are involved in appetite regulation [55,56,61]. Moreover, improving satiety, fiber ingestion could determine a lower caloric intake at the next meal, with potential impacts in reducing weight gain [55,62]. Administration of fiber-rich supplements composed by polysaccharide macromolecules such as cellulose, hemicellulose, pectin and mucilage acts via generation of a network of soluble and insoluble fibers typically not absorbed by the body and intends to reduce the absorption of carbohydrates and lipids from the diet, thus reducing the extent and speed of the increase in glycaemia after meals, and leveling out the concentration of blood glucose and insulin [62–64]. As reported recently, in animals those mechanical features are known to improve parameters defining metabolic syndrome such as weight gain, insulin sensitivity and serum markers levels in a high fat diet fed mouse. Moreover, polysaccharide macromolecules supplementation has induced specific liver gene

Table 2
Reference age, dosage and duration of administration of bioactive compounds in clinical trials and meta-analysis targeting the paediatric population.

Bioactive compound	Author (year of publication), study design	Dosage under investigation	Duration of administration	Reference age
Polysaccharide Macromolecules	Stagi et al. (2015), RCT[67] Stagi et al. (2017), retrospective study[68] Fornari et al. (2020), RCT[65]	• 2175 mg (three tablets) of a high-fiber raw mixture (glucomannan (*Amorphophallus konjac*), cellulose, Opuntia pulp stem (*Opuntia ficus indica*), chicory root (*Cichorium intybus*), freeze-dried mallow root mucilage (*Althaea officinalis*), freeze-dried flaxseed mucilage (*Linum usitatissimum* L) and freeze-dried linden flower mucilage (*Tilia platyphyllos Scop*)[67,68] • 1450 mg (two tablets) of the same high-fiber raw mixture[65]	12 months 20 min before mixed meal consumption	School-age children and adolescents (8–16 years) School-age children (8–12 years)
Omega-3	López-Alarcón et al. (2011), RCT[73] Nobili et al. (2011), RCT[79] Nobili et al. (2014), clinical trial[80] Pacifico et al. (2015), RCT [81] Janczyk et al. (2015), RCT [82]	• 360 mg DHA + 540 mg EPA daily[73] • 250–500 mg/day of DHA[79–81] • 450–1300 mg/day EPA+DHA[82]	1 month 6–18 months 24 weeks	Children and adolescents (9–18 years) Children and adolescents (<18 years) Children and adolescents (5–19 years)
Vitamin D	Alves et al. (2021), RCT[100] Cai et al. (2021), meta-analysis of RCT[99] Hauger et al. (2020), meta-analysis of RCT[101] Sacheck et al. (2022), RCT [102] Belenchia et al. (2013), RCT [103]	• 1000 IU/day[100] • Ranges from 400 IU/day to 50,000 IU/week[99] • 10–125 μg/day up to 1250–7500 μg/week[101] • 600–2000 IU/day[102] • 4000 IU/day[103]	12 weeks From 6 weeks to 6 months From 4–6 weeks 6 months 6 months	School-age children (4–11 years) Children and adolescents Children and adolescents (4–19 years) Children and adolescents (8–15 years) Children and adolescents (9–19 years)
Prebiotic	Nicolucci et al. (2017), RCT [108] Visuthranukul et al. (2022), RCT[109,110]	• 8 g/day oligofructose-enriched inulin[108] • 13 g/day extract-inulin[109,110]	16 weeks 3 months	School-age children (7–12 years) School-age children and adolescents (7–15 years)
Probiotic	Mohammadi et al. (2019), meta-analysis[114] Solito et al. (2021), RCT[115] Chen et al. (2022), RCT[116]	• Different combinations evaluated[114] • 2 × 10^9 CFU/AFU/day of *Bifidobacterium breve* BR03 and B. *breve* B632[115] • *Lactobacillus salivarius* (10^9 CFU), *L. rhamnosus* bv-77 (10^9 CFU), and *Bifidobacterium animalis* (8 ×10^9 CFU) [116]	4–16 weeks 8 weeks 12 weeks	Children and adolescents (2–18 years) School-age children and adolescents (6–18 years) School-age children and adolescents (6–18 years)
Synbiotic	Mohammadi et al. (2019), meta-analysis[114] Kilic Yildrim et al. (2022), RCT[117]	• Different combinations evaluated[114] • Probiotic mixture including *Lactobacillus acidophilus, Lacticaseibacillus rhamnosus, Bifidobacterium bifidum, Bifidobacterium longum, Enterococcus faecium* and fructo-oligosaccharides)[117]	4–16 weeks 12 weeks	Children and adolescents (2–18 years) School-age children and adolescents (8–17 years)
Polyphenols				
Curcumin	Saraf-Bank et al. (2019), RCT [172]	500 mg/day[172]	10 weeks	Adolescents (13–18 years)
Chlorogenic acid		* no data in pediatric age 200–400 mg/day in adults		
Quercitin		* no data in pediatric age 100–150 mg/day in adults		
Phlorizin		* no data in pediatric age 1,35–1,8 g/day of apple extract in adults		
Berberine		* no data in pediatric age 300–1000 mg/day in adults		
Bromelaine		* no data in pediatric age for metabolic purpose 250–2000 mg/day in adults		
D-chiro-inositol (DCI) and Myo-Inositol (MI)	Mancini et al. (2016), clinical trial[198]	MI 1100 mg + DCI 27.6 mg daily[198]	6 months	School-age children (7–15 years)
Alpha-lipoic Acid	Tromba et al. (2019), RCT [216] El Amrousy et al. (2020), RCT [217]	600–800 mg/day[216,217]	3 months	School-age children and adolescents (8–18 years)

Abbreviations: Randomized Controlled Trial (RCT); Docosahexaenoic acid (DHA); Eicosapentaenoic acid (EPA); International Unit (IU); Colony-Forming Unit (CFU); Active Fluorescent Units (AFU); Myo-Inositol (MI); D-chiro-inositol (DCI)

expression in mice, by upregulating several genes associated with glucose homeostasis, insulin signaling and lipid metabolism while downregulating genes involved in lipid storages. Following this, it has been shown a positive role in rescuing circulating levels of Insulin-like growth factor binding proteins (IGFBPs) in mice [63].

In RCT involving 46 obese Caucasian children, a significantly lower increase in postprandial triglycerides and appetite has been found in children who received polysaccharide macromolecules supplementation 20 min before receiving a mixed meal (calculated as 15 kcal/kg of FFM), compared with children who assumed placebo. Moreover, a significant reduction in ghrelin was found in the postprandial period in obese children [65].

Interestingly, another RCT found polysaccharide macromolecules treatment being successful as a metformin treatment on 100 adult patients with T2D or metabolic syndrome. Surprisingly, the effects of metformin on glucose metabolism consisted of a comparable, significant reduction in glycated hemoglobin (HbA1c), C-peptide, fasting plasma glucose (FPG), and HOMA-IR compared with the baseline. Similarly, both treatments, in association with a Low Glycemic Index-diet, induced a significant, comparable reduction in body mass index (BMI) and waist circumference. Conversely, the response of the lipid parameters (total cholesterol, LDL cholesterol, triglycerides) was different; the effect of metformin combined with diet was modest after six months, while a polysaccharide macromolecules supplementation combined with diet was significantly more pronounced already at three months and even more at six months [66].

In addition, Stagi et al. conducted a clinical study on 133 children with obesity, excluding those with T2D, use of medications known to promote weight gain or loss, secondary obesity, or chronic diseases. They were randomly allocated in tree arms: A. Low Glycemic Index-Diet plus polysaccharide macromolecules supplementation, B. Low Glycemic Index-Diet, C. Energy Restricted Diet. They observed a significant reduction in HbA1c and Acanthosis Nigricans in arms A and B. At T1 the BMI z score value significantly reduced from 2.32 to 1.80 ($p < 0.0001$) in Arm A and from 2.23 to 1.99 ($p < 0.05$) in Arm B. The HOMA-IR index was significantly reduced in Arm A ($p < 0.0001$) and B ($p < 0.05$), with Arm A showing a significant reduction in the insulinogenic index ($p < 0.05$) and overall patients showing glucose metabolism abnormalities such as IGT or T2D experienced better glycemic metabolism [67].

Lastly, Stagi et al. reported that 71 obese children and adolescents treated for one year with the same supplement added to metformin had a significantly larger reduction in BMI standard deviation score and glucose metabolism improvement compared with peers treated with metformin ($n = 58$) or diet alone ($n = 51$) [68]. The same authors, in another retrospective study on 27 pediatric patients with a diagnosis of type 1 diabetes in conjunction with obesity and metabolic syndrome, reported improvements in glucose metabolism. The group of children treated with polysaccharide macromolecules showed a significant reduction in BMI standard deviation (SD) score ($p < 0.005$), waist circumference SD score ($p < 0.005$), glycated hemoglobin ($p < 0.05$) and daily mean insulin dose requirement ($p < 0.005$)[69].

The use of polysaccharide macromolecules supplements, especially if associated with appropriate dietary changes, may help to achieve treatment targets in children with metabolic disorders. Their potential role should be confirmed with additional studies in the pediatric population, evaluating if dietary fiber supplements positively impact the gut microbiome and its metabolites, with possible beneficial effect against cardiometabolic risk factors.

3.2. Omega-3

Omega-3 fatty acids are polyunsaturated fatty acids (PUFA) considered essential for the human body. In particular, their precursor, alpha-linolenic acid (ALA), is not synthesized and must be introduced through food. Their main sources are vegetable oils rich in linolenic acid and fish oils rich in docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) [70]. ALA intake should meet the daily energy requirement of 0.5% in pediatric age. In addition, 250 mg per day of EPA and DHA are recommended, and children aged 1–2 years should receive an additional dose of 100 mg per day of DHA [71]. According to the European Food Safety Authority (EFSA) [72], if taken during pregnancy, omega-3 contribute to the fetal development since they have a beneficial effect on vasodilation and anti-inflammatory properties. Furthermore, they have beneficial effects on increased insulin sensitivity and weight reduction in obese patients [73]. However, it is unclear whether the two effects are interdependent and whether the same effect occurs in children. Some results seem to inversely relate the serum concentration of omega-3 to the severity of pediatric obesity [74–77]. This established the basis for the evaluation of omega-3 supplementation in the pediatric population with obesity and metabolic syndrome. Previous studies evaluated omega-3 long-chain PUFA intake in obese and insulin-resistant children and demonstrated beneficial effects on insulin resistance regardless of weight [73]. However, a meta-analysis of RCTs subsequently stated that omega-3 supplementation does not alter anthropometric indices in children and adolescents, necessitating further studies with larger pediatric samples [78].

Omega-3 supplementation has been proposed as a treatment for non-alcoholic fatty liver disease (NAFLD) in children. An improvement of liver ultrasound findings at 6 months was confirmed at the 18-month biopsy with reduction of steatosis, lobular inflammation and ballooning [79,80]. Moreover, the hepatic fat fraction (HFF), assessed by magnetic resonance spectroscopy, was significantly decreased in children after 6 months of DHA intake [81]. However, conflicting data are still recorded on the reduction of alanine aminotransferases (ALT) and BMI in children with NAFLD [79,80,82]. Lastly, some data suggest an improvement in the carotid intima thickness and cardiometabolic markers, suggesting omega-3 as a predictor of cardiovascular risk among children with NAFLD [83].

Although the sample was heterogeneous and small, an improvement in endothelial function, vascular structure and metabolic parameters was shown in adolescents with type 1 diabetes mellitus (DMT1) [84]. Future studies are needed to confirm the cardiometabolic effects of DHA supplementation and evaluate the efficacy of DHA on prevention and management of complications in children and adolescents with DMT1.

In terms of specific reduction in lipid balance, fish oil intake was associated with a non-statistically significant reduction in triglycerides and the triglyceride/high-density lipoprotein (HDL) ratio. No effect on HDL-cholesterol, non-HDL-cholesterol and total cholesterol was reported [85].

Finally, no beneficial effects of omega-3 supplementation were found on arterial structure and function and subsequently on blood pressure in the pediatric population [86]. In conclusion, omega-3 supplementation has shown beneficial effects on IR and hepatic steatosis in children with NAFLD. However, the effect on other cardiometabolic parameters deserves further study.

3.3. Vitamin D

Vitamin D is a fat-soluble vitamin which plays a significant role in calcium homeostasis and bone metabolism. Although few foods naturally contain vitamin D (fatty fish, such as sardines, herring, tuna, mackerel, salmon and cod liver oil, egg yolks, shiitake mushrooms, liver or organ meats), skin synthesis as a result of ultraviolet-B (UVB) radiation remains the main natural source of this vitamin in humans [87]. Vitamin D from diet or skin synthesis is biologically inactive, so it is enzymatically converted in the liver into 25-hydroxyvitamin D, the main circulating form, and then in the kidney into 1,25-dihydroxyvitamin D, the active form of vitamin D. Although the recommended dietary intake of vitamin D for infants up to 12 months (400 IU daily) and for children aged 1–18 years (600 IU daily) is well known, the prevalence of hypovitaminosis D remains at high levels among the pediatric population

[88–90].

Several pathophysiological mechanisms have been proposed to explain the interdependence between serum vitamin D levels and metabolic syndrome components. Firstly, vitamin D deficiency may inhibit the conversion of pro-insulin to insulin resulting in impaired insulin secretion and sensitivity [91]. Serum vitamin D levels are inversely correlated with the concentration of HbA1c [92]. Furthermore, vitamin D may exert an influence on metabolism resulting in a decrease in cholesterol synthesis [93]. However, obesity may also reduce serum vitamin D levels through the accumulation in the adipose tissue, resulting in an increased volumetric dilution [94,95].

A RCT found a correlation between improved serum vitamin D levels in obese adolescents on a weight loss program and a reduction in carotid intima-media thickness, a well-known marker of atherosclerosis [96]. However, several studies regarding the impact of vitamin D supplementation on the reduction of body mass in overweight and obese children did not found statistically significant beneficial effects. No significant reduction in BMI and changes in body composition or bone mineral density were found [97]. A follow-up study confirmed the absence of significant results on BMI, although significant reductions in diastolic blood pressure, waist circumference and fasting blood glucose, total cholesterol and LDL cholesterol were observed among adolescent girls taking vitamin D supplementation for nine weeks [98].

Conflicting data result from the evaluation of the impact of vitamin D supplementation on the lipid profile. A recent meta-analysis found that vitamin D supplementation causes a significant reduction in triglycerides and fasting glucose in pediatric patients under supplementation. However, no beneficial effects were demonstrated on other cardiometabolic markers including high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol, BMI, waist circumferences, systolic blood pressure and diastolic blood pressure [99]. A further placebo-controlled study was conducted in normal-weight, overweight and obese children with hypertriacylglycerolemia and both sufficient and insufficient basal vitamin D levels. The results confirmed the effects on the lipid profile, in particular a significant reduction in total cholesterol, LDL-C, HDL-C and total cholesterol/HDL-C ratio was observed in children with hypertriglyceridemia, even if in absence of beneficial effects on the body composition [100]. However, another meta-analysis found that vitamin D supplementation does not influence the lipid profile depending on the BMI [101]. An RCT examined supplementation with different vitamin D dosages on cardiometabolic risk factors among normal-weight, overweight and obese children at risk of deficiency. A significant increase in HDL-C as well as a significant decrease in LDL-C and total cholesterol, especially at the lower dosage of 600 IU/day, were found [102].

Lastly, the link between vitamin D and insulin resistance is well known. Increased circulating vitamin D concentrations were found to be associated with improved markers of insulin sensitivity and resistance among obese adolescents. Therefore, vitamin D supplementation may be beneficial when combined with standard treatment of obesity and associated insulin resistance [103].

In conclusion, the relationship between vitamin D deficiency and the components of metabolic syndrome remains a controversial issue. Although the beneficial effects on fasting blood glucose and IR are well known, the effects on the lipid profile need for further studies, and the remaining cardiometabolic parameters lack of conclusive scientific evidence.

3.4. Biotics

Interestingly, RCTs involving the gut microbiota are significantly increasing, due to the possible impact in reducing inflammation and metabolic disorders in obese subjects. Apparently, gut microbiota in children has been shown to be more flexible to environmental changes rather than in children, and this population might respond promptly to microbiota-based interventions, which may reverse deleterious metabolic conditions [43]. Microbiome-based interventions imply the modulation of gut microbiota through the provision of prebiotic, probiotic, synbiotic or postbiotic. All of these supplements confer a health benefit on the host, particularly prebiotics are substrates that are selectively utilized by host microorganisms [104], while probiotics are live microorganisms administered in adequate amounts [105], and synbiotics are a mixture of both live microorganisms and substrates selectively utilized by host microorganisms [106]. Regarding prebiotics, Liber et al. studied the effect of a prebiotic oligofructose for 12 weeks in Polish overweight and obese children and adolescents. They found no differences in the treated group compared to placebo, however drop-out rates were high [107]. After that Nicolucci et al. investigated the effect of oligofructose-enriched inulin (OI) or maltodextrin placebo, once daily for 16 weeks in a group of obese Canadian children aged 7–12 years. Participants assuming OI showed a slower weight gain compared to placebo, and after treatment total fat mass was significantly lower compared with placebo [108]. Instead, a recent RCT showed a significant increase in fat-free mass in a group of Thai obese children treated with inulin-extract for 3 months, both compared with placebo and dietary fiber-only advice group. BMI z-score, fat mass index (FMI), and trunk FMI improved in all groups and no significant differences between groups were observed. Thus, authors speculated that the possibility that inulin supplementation could be beneficial in pediatric obesity management without intensive behavioral modification cannot be ruled out [109,110]. Regarding the actual effect of prebiotics on metabolic health, evidence is poor in obese children [108,109], in spite of adults, in which a meta-analysis found a significant reduction in fasting glucose and fasting insulin after the assumption of soluble fiber supplementation [111]. Nicolucci et al. found a significant decrease in serum triglycerides within the prebiotic group, but no differences in lipid profile. However, the prebiotic group experienced a reduction in *Ruminococcus gauvreauii* and *Bacteroides vulgatus,* which positively correlated with the changes in trunk body fat and serum triglycerides respectively, that were observed in the prebiotic group [108].

Among probiotic strains, *Lactobacillus* and *Bifidobacterium* species are the most commonly used as supplementations. The effectiveness of probiotic and synbiotic supplementation was reported to improve dyslipidemia and various metabolic parameters among adult subjects with hypercholesterolemia and hypertriglyceridemia, prediabetes, type 2 diabetes, fatty liver, and metabolic syndrome [112,113]. However existing evidence on their possible effects in pediatric age has not been fully established. A meta-analysis evaluated the effects of 4–16 weeks of pro-/synbiotic supplementation on anthropometric indices, fasting blood glucose, and lipid profiles (LDL-C, HDL-C, total cholesterol, triglycerides) in overweight or obese children and adolescents [114]. The analysis of 9 selected studies did not found any significant change in the variables of interest in the treated group compared to control. Instead, a subgroup analysis revealed a significant reduction in BMI z-score within the synbiotic supplementation. Authors concluded that a diversity of probiotic's strains were employed between studies, each with a different predicted impact on the microbiota, thus large scale studies are warranted to confirm present findings [114]. Three well-designed RCTs were then carried out in the pediatric population [115–117]. Solito et al. investigated the effect of probiotic supplementation with *Bifidobacterium breve* BR03 and *B. breve* B632 in a group of 101 subjects (6–18 years old) with obesity and insulin-resistance. After 8 weeks of intervention probiotic cohort's mean values were lower than the placebo ones for waist circumference (-3.41 cm, $p < 0.05$), BMI z-score (-0.17 kg/m^2, $p = 0.07$), fasting insulin (-4.57 mcUI/ml, $p < 0.06$), and ALT (-3.64, $p < 0.05$). Moreover, probiotic treatment improved insulin sensitivity at fasting (QUICKI index, 0.013 $p = 0.05$) [115]. In another, 82 Chinese children with obesity were allocated to receive either probiotic supplement with *Lactobacillus salivarius*, *L. rhamnosus* bv-77, and *Bifidobacterium animalis* vs. placebo for 12 weeks. Overall, the reduction in the BMI level was significantly greater in the probiotic group ($p = 0.026$). The blood lipid content significantly changed in the probiotic group, and

LDL and HDL significantly differed ($p < 0.05$) [116]. A double-blind RCT in 61 obese children aged 8-to-17 years old receiving synbiotic supplement (probiotic mixture including *Lactobacillus acidophilus, Lacticaseibacillus rhamnosus, Bifidobacterium bifidum, Bifidobacterium longum, Enterococcus faecium* and fructo-oligosaccharides) found a significant change in body weight, BMI, waist circumference and waist circumference-to-height ratio when compared with placebo. Instead, no difference in glucose metabolism, lipid parameters, presence of non-alcoholic fatty liver disease were found [117].

Future studies should evaluate the potential effects of an early probiotic administration in pregnant women and infants. According to a recent systematic review, current evidence on this topic is inadequate, as no studies on early probiotic administration for prevention of metabolic syndrome were found, and the two follow up studies conducted so far did not focus on high-risk infants [118].

Lastly, postbiotics are a "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host". They contain inactivated microbial cells or cell components, with or without fermentation products and metabolites [119]. Up to date, pediatric population, especially the neonatal one, seems to be a suitable target for studying the positive effects of postbiotics [120,121]. On the contrary, in children with obesity and related comorbidities no evidence of efficacy is available as studies are ongoing [44].

Overall, the administration of biotics is a promising tool when combined with dietary intervention and lifestyle modification in children with metabolic derangement. Considering that the effects of probiotics and synbiotics are strain specific and host specific, selection of probiotics is an important issue and no specific pediatric recommendations have been developed for the clinical practice.

3.5. Polyphenols

Polyphenols are a heterogeneous group of natural substances produced by the secondary metabolism of plants. They are composed of flavonoids (such as flavanols, anthocyanidins, anthocyanins, isoflavones, etc.) and non-flavonoids (such as phenolic acids, stilbenes, and lignans) [122]. Polyphenols can be naturally found in a wide variety of fruits, vegetables, grains and beverages (tea and wine, mostly) [122,123]. The dietary pattern that is richer in polyphenols seems to be the Mediterranean one (average daily intake is estimated at 700 mg/day), characterized by large portions of vegetables, daily use of olive oil, frequent consumption of nuts and a moderate consumption of red wine [124]. Western Diet is estimated to provide 300–1100 mg/day of polyphenols [123].

The best-known biological action of polyphenols is undoubtedly their antioxidant capacity, guaranteed by the chemical structure of their molecule, whose aromatic ring acts as an electron donor [122]. Studies in vitro or in animal models correlate the antioxidant capacity of polyphenols with a reduction in the generalized inflammatory state known to underlie metabolic syndrome and obesity [123]. Other mechanisms, by which polyphenols are known to reduce obesity and metabolic syndrome, are the ability to activate fatty acid beta-oxidation processes, induce satiety, inhibit adipocyte differentiation, promote adipocyte apoptosis and stimulate lipolysis [124,125]. Evidence in the human population, however, is poor and often inconclusive. Several epidemiological studies have shown an inverse association between polyphenol intake and obesity [126,127]. However, most of these studies assess polyphenol intake by means of questionnaires on dietary habits and not by measuring the amount of polyphenol intake and specifying the type of polyphenol. The same limitation can be found in most of the interventional studies conducted so far; moreover, the results are often only significant in the healthy population or those with early obesity and become inconsistent when applied to obese subjects or those with an established metabolic syndrome [123–125,128]. Observational studies on the inverse correlation between a prolonged Mediterranean diet (naturally rich in polyphenols) and obesity were conducted [129–135]. Unfortunately, most studies conducted on humans only involved adults. Even though, the 'HELENA' study found an inverse correlation between polyphenol intake and BMI in a population of 657 adolescents, 14.8% of whom were overweight. Moreover, a recent clinical study correlated cherry-derived polyphenol supplementation with the inhibition of spontaneous osteoclastogenesis, typical of obese children [136].

3.5.1. Chlorogenic acid

Chlorogenic acid ingested with food is hydrolyzed in the gastrointestinal tract into caffeic acid and quinic acid by bacterial esterases; about one third is then absorbed in the small intestine, while the remaining two thirds are absorbed in the colon [137].

The biological effects of chlorogenic acid appear to be mediated by its metabolites, in particular caffeic acid, dihydrocaffeic acid, hippuric acid, felluric acid, vanillic acid and benzoic acid [138].

The food that contains most chlorogenic acid is green coffee. Other foods are apples, blueberries, peaches, pears, plums, tomatoes, eggplants, peanuts and potatoes. It seems to function as an antioxidant, glycemic control agent, anti-hypertensive, anti-inflammatory, antimicrobial, neuro-protective and anti-obesity agent. It activates the AMP activated protein kinase, inhibits 3-hydroxy 3-methylglutaryl coenzyme-A reductase and strengthens the activity of carnitine palmitoyl-transferase to control the obesity [139,140].

Concerning the use of chlorogenic acid in patients with metabolic syndrome, there is no data on pediatric age. In adults, instead, 400 mg/day of chlorogenic acid derivatives were administered to patients suffering from metabolic syndrome for 8 weeks, finding a reduction in blood pressure, fasting glycaemia, waist circumference and appetite [141]. Similar results emerged from the trial by Patti et al. [142]. A 6 months RCT evaluated the efficacy on hepatic and cardiometabolic parameters of subject suffering from metabolic syndrome of a food supplement (chlorogenic acid and luteolin), finding an improvement in body weight, waist circumference, HbA1c, plasma lipids, hepatic transaminases and carotid intima-media thickness [143].

Similarly, there are no studies to date on the pharmacological use of chlorogenic acid in the treatment or prevention of pediatric obesity. Thom et al. showed that after 12 weeks of a diet rich in chlorogenic acid (200 mg/day), weight loss in 30 overweight adults was significantly higher [144]; similar results were found by Dellalibera et al. [145]. Bakuradze et al. demonstrated a significant reduction in body weight associated with the intake of coffee enriched with chlorogenic acid [146]. Positive results on the reduction of body weight also emerged from a meta-analysis and a recent systematic review [147,148], with beneficial effects on weight reduction, BMI and waist circumference. Nonetheless, no effects were found on the weight reduction in other two studies [149,150].

3.5.2. Quercetin

Quercetin belongs to the flavonoid family. It cannot be found in nature in an isolated form but as an aglycone (non-sugar component) of several glycosides, such as rutine and quercitrin. It is found in a wide variety of fruits, vegetables, beverages such as tea and red wine [151].

Pharmacokinetics and bioavailability of this nutraceutical are mostly unknown; however, its glycosylated form (naturally contained in food) appears to be more easily absorbed than isolated quercetin. The absorption capacity of quercetin in the gastrointestinal tract also varies depending on its solubility, which is modified by the presence of ethanol, fats and emulsifiers [151,152].

The biological effects of quercetin appear to be anti-oxidant, antimicrobial, anti-carcinogenic, anti-hypertensive and anti-obesity [151]. In particular, quercetin's action against obesity is on the expression and transcription of genes involved in the regulation of lipogenesis [153,154].

There are no studies conducted on children. Lee et al. showed that the administration of 100 mg/day of quercetin in obese adults correlated with a significant reduction in BMI and fat mass [155]. Two other

studies found that the intake of 150 mg/day of quercetin was correlated with a reduction in abdominal circumference in obese subjects [156, 157]. On the contrary, Egert et al. found no changes in the nutritional status of overweight or obese patients treated with 150 mg/day of quercetin for 6 weeks [158]. However, a recent review concluded that quercetin may reduce cardiovascular risks via modulation of lipid profile, blood glucose, and insulin resistance [159]. Another review collecting three RCTs found that quercetin can improve ovulation disorder, relieve IR, reduce androgen, regulate lipid metabolism, regulate gut microbiota and improve vascular endothelial function [160].

3.5.3. Phlorizin

Phlorizin (also called phloridzin) is a glycoside of phloretin, which belongs to the class of flavonoids (polyphenols). It is mainly found in unripe apples, and small traces have also been found in strawberries [161]. Like most polyphenols, it has a low bioavailability.

Phlorizin is commonly known to be a competitive inhibitor of sodium-glucose co-transporters SGLT1 and SGLT2; its action in reducing renal reabsorption and intestinal absorption of glucose with consequent reduction of blood glucose levels and application in the field of diabetes is therefore well known. Other well-known properties of phlorizin, demonstrated in preclinical studies, are its anti-oxidant and anti-inflammatory activities [162].

There are currently no clinical studies in the pediatric population evaluating the use of phlorizin in the treatment of obesity. A RCT has been conducted on adults consuming drinks enriched with a phlorizin apple [163]. Phlorizin-rich apple extract significantly reduced glycemia after 30 min at all doses, while the gastric emptying time and urinary glucose excretion did not differ. Dose-dependent treatment effects were observed for insulin, C-peptide, and glucose-dependent insulinotropic polypeptide.

3.5.4. Curcumin

Preclinical studies suggest that curcumin, a polyphenol contained in turmeric, has the ability to inhibit fatty acid synthesis and reduce fat reserves [125]. Mechanistically, curcumin and its analogues like hexahydrocurcumin and tetrahydrocurcumin have been reported to elicit anti-hypertensive effects through diverse signaling pathways [164]. Curcumin may have therapeutic effects on metabolic syndrome through various genetical pathways, targeting genes such as NOS3, IL6, INS, and ADIPOQ, particularly PPARγ [165].

Chuengsamarn et al. found an improvement on β-cells (higher HOMA-β, lower C-peptide, lower level of HOMA-IR and higher adiponectin) of 240 prediabetic subjects supplemented for 9 months [166]. On the contrary, Naseri et al. did not found additional cardiometabolic benefits in 52 patients with NAFLD receiving 1.5 g of curcumin per day [167].

However, systematic reviews and meta-analyses state that curcumin improves oxidative and inflammatory status in patients with metabolic syndrome [168–171], with beneficial effects on the glycemic control and the lipid metabolism in patients with PCOS, without significant adverse effects [170]. It may also lower fasting plasma glucose and HbA1c, triglyceride, total cholesterol, and LDL [169,171]. Lastly, it seems that products derived from the ingestion of curcumin and those produced by the gut microbiota may play a role [171]. The only RCT conducts on a pediatric population of overweight adolescents found a positive effect of curcumin on BMI and waist circumference [172].

3.5.5. Berberine

Berberine, an isoquinoline alkaloid, can be found in many commonly used botanicals [173]. Berberine has been related with many functions on cardiovascular and metabolic diseases, such as blood glucose and lipids regulation and antidiabetic action [174]. It promotes glucose transport and consumption, lipid metabolism impacting lipid synthesis, increases anti-inflammatory cytokines secretion, alleviates low chronic inflammation, suppresses oxidative stress [175,176]. Berberine seems to increase the gut microbiota barrier function, reducing the local inflammation and regulating the bile acid signal pathway [177]. Berberine supplementation benefits on inflammatory markers related to metabolic syndrome, PCOS and obesity have been searched in adults [178–181]. Results found that berberine improved some of the metabolic and hormonal derangements in PCOS women, had a beneficial impact on gene regulation for the absorption of cholesterol at a dose of 300 mg/day, and was capable of modulating the diversity of gut microbiota at the dose of 500 mg/day [178–181].

3.6. Bromelain

Bromelain is a proteolytic enzyme contained in the flesh but mainly in the stem of the pineapple. Eight different bromelain fractions, with different chemical formulas, have been identified; however, in clinical practice, bromelain in its natural form is generally used [182]. The gastrointestinal absorption of bromelain after oral administration is 40%; its plasma half-life is approximately 6–9 h. The therapeutic dosage of bromelain in the adult population is generally considered to be 250–2000 mg/day, to be divided into 2–3 daily doses [183,184].

The best-known properties of bromelain, related to its action as a proteolytic enzyme, are digestive, anti-inflammatory and anti-edematous. Its use, in addition to its anti-dyspeptic function, is therefore prevalent in orthopedics, as an adjuvant in the treatment of inflammatory states of soft tissue. Other known actions of bromelain are its keratolytic action, exploited for the topical treatment of burns, and its anti-thrombotic and fibrinolytic action, used for the treatment and prevention of cardiovascular disease [182,183]. However, very few studies are available. For instance, Dave et al. found that bromelain inhibits adipocyte differentiation in vitro by reducing the expression of adipogenic genes and inducing the apoptosis of mature adipocytes. The inhibition of the adipogenesis seems to be mediated by a modulation of the PPARγ pathway, while the pro-adipolysis action is mediated by stimulation of the TNFα pathway [185]. There are currently no studies about the use of bromelain in the treatment of obesity in children. However, the bromelain molecule is already used in pediatric settings for its mucolytic, anti-congesting, and keratolytic properties [186–188].

3.7. Inositols

D-chiro-inositol (DCI) and Myo-Inositol (MI) are two stereoisomers of inositol, easily found in plant based diets and considered insulin sensitizers [189]. Liver plasma membrane releases inositol phosphoglycans (IPGs) under insulin stimulation and activation of a phosphatidyl-inositol-specific phospholipase C. Those IPGs seems exert an insulin-mimetic activity, acting as second messengers downstream of insulin receptors [189].

The current target population highlighted for inositol clinical trials are PCOS women. Indeed, several trials have found their role in improving insulin sensitivity, blood pressure, plasma triglycerides concentrations and decrease ROS production in follicular fluid and consequent reduction of IR [190–195]. This compound may be useful especially for female adolescents with PCOS diagnosis [196]. Only one trial has tested the effects of inositol along or in combination with oral contraceptives (OCP) on PCOS teenagers. They stated that a therapy based on this natural compound alone or in combination with OCP seems effective to improve both metabolic and hormonal parameters of PCOS adolescents and thus could represent a novel and valid option to consider for the treatment of this syndrome [197]. An RCT conducted on 11 male children with obesity supplemented with inositol for 6 months (MI 1100 mg + DCI 27.6 mg + folic acid 400 μg) found a significant reduction in fasting insulin as well as both blood glucose and insulin after 120 min [198].

3.8. Alpha-lipoic Acid

Alpha-lipoic acid (α-LA), also known as thioctic acid, a short-chain fatty acid, is synthesized in mitochondria by the lipoic acid synthase system and is also naturally occurring in small amounts in plant foods (broccoli, spinach, potatoes, yeast, tomatoes, Brussels sprouts, carrots, beets, and rice bran) or animals derived dietary sources (liver and red meat) [199]. The endogenously synthesized α-LA plays a crucial role in many metabolic functions, biological activities, mitochondrial enzymes, and cellular respiration. The proposed mechanisms of action involves Akt phosphorylation together with AMPK and SIRT1 signaling pathways [200–203].

Studies supported the use of lipoic acid in the treatment of obesity and metabolic syndrome, with benefits on weight and BMI loss, reduction of hepatic steatosis, decrease in average blood pressure values and improvement of the lipid and glycemic profile in adult population [204–211]. A recent meta-analysis evaluated the effect of α-LA supplementation on cardiometabolic risk factors in adult patients with type 2 diabetes. Authors found that each supplementation of 500 mg/day oral α-LA significantly reduced HbA1c and body weight [212]. Results are in line with previous meta-analysis on various populations, including patients with metabolic syndrome, stroke, and non-alcoholic fatty liver disease [213–215]. Clinical trials are emerging also in pediatric cohorts. Tromba et al. randomly assigned to oral supplementation with α-LA (800 mg/day) 67 overweight/obese children. After a three-month treatment, no significant differences within and between each group for anthropometric and metabolic variables were found. Even though, they found interesting results on markers of cardiovascular risk, since treatment with α-LA was associated with significant increases in basal and peak arterial diameters, at values comparable to the ones observed in a group of normal-weight healthy subjects. Those results indirectly point out a better vascular tone and endothelial function, which are known to be a key parameter also in the prevention of metabolic syndrome [216]. After that, in another trial a group of 80 obese children were randomized to receive 600 mg/day of α-LA. The treated group showed a significant reduction of weight, BMI, malondialdehyde (a marker for the amount of oxidative stress), TNF-α, and leptin levels, but a significant increase of adiponectin level ($p < 0.05$) compared with the control group. However, it had no effect on fasting blood glucose or lipid profile ($p > 0.05$) [217].

Alpha-lipoic acid administration has been reported to be safe and well-tolerated in adults, with very few side effects described in the literature [218]. Even though, little information is available regarding children. Sporadic episodes of alpha-lipoic acid intoxication have been reported in some *case reports* in children [219–222].

In conclusion, studies conducted on the pediatric population seems to be encouraging, even if it is not possible to define with certainty the efficacy of using lipoic acid in the treatment of obesity and metabolic syndrome.

4. Conclusions

Bioactive compounds can be considered an effective complementary solution to dietary therapy, offering a significant help in the management of obese children and adolescents (Fig. 2). Some types of bioactive compounds have been investigated for the management of MUO (Table 2). Given the nature of these molecules, their potential role may be remarkable as they could be suggested as adjuvant therapy after a

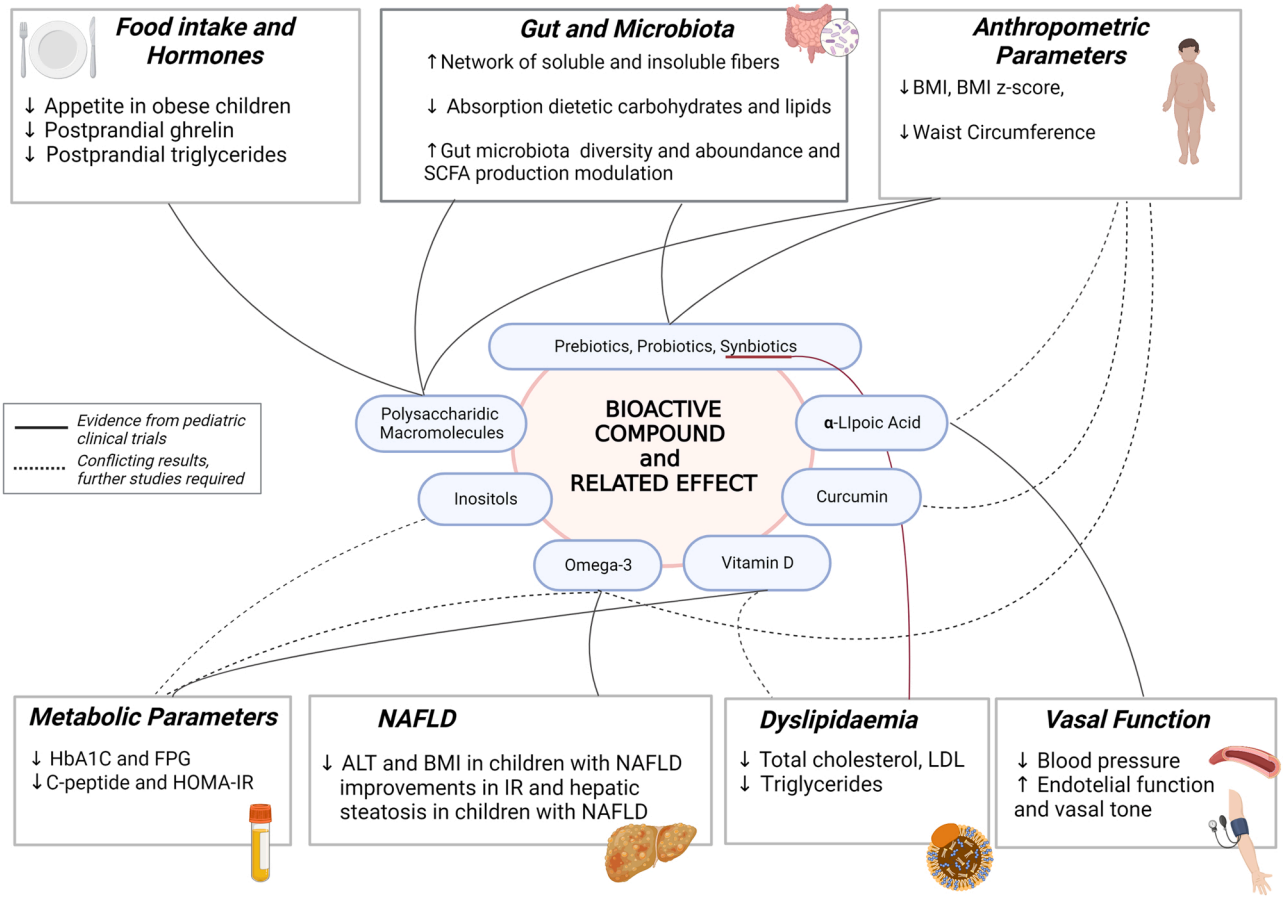

Fig. 2. Bioactive compounds under investigation and related health effects in pediatric obesity. Abbreviations: *Short Chain Fatty Acids (SCFA); Body Mass Index (BMI); Glycated haemoglobin (HbA1c); Fasting Plasma Glucose (FPG); Homeostasis Model Assessment of Insulin Resistance (HOMA-IR); Nonalcoholic Fatty Liver Disease (NAFLD); Alanine Aminotransferase (ALT); Insulin Resistance (IR); Low-density Lipoprotein cholesterol (LDL).*

personalized dietary counseling or a medical doctor consultation.

Among bioactive compounds, omega-3 and vitamin D represent the most investigated ones in the pediatric age. Although conflicting results, vitamin D is of particular interest for the modulation of glucose metabolism, whilst omega-3 are increasingly studied in pediatric age groups affected by NAFLD. However, dosages under investigation are overly heterogeneous. The growing interest in the axis between metabolic health and gut microbiota led to the dissemination and use of biotics supplements and polysaccharide macromolecules. Prebiotics, probiotics and polysaccharidic compounds have been studied for their effects on anthropometric indices and the regulation of satiety. In addition, synbiotics have shown a positive impact on the lipid metabolism of obese children and adolescents. Polyphenols remain the most diverse group of bioactive substances with important preclinical evidence. Nevertheless, the evidence of their effect on the pediatric population is absent so far, with the exception of curcumin. Lastly, inositols and alpha-lipoic acid should not be disregarded as novel bioactive compounds with potential cardio-metabolic effects.

Further studies on larger pediatric populations are then needed to better clarify optimal doses and specific effects of each bioactive compound on obesity and its implications, such as the metabolic syndrome. Recommendations for their clinical application have not been developed yet. However, it is undoubtedly crucial to emphasize that dietary supplements, including bioactive molecules, should never be considered as an alternative to diet or lifestyle changes, which still represent the cornerstone of treatment in the pediatric obesity.

Funding

This research received no external funding.

CRediT authorship contribution statement

Giulia Fiore: Investigation, Writing – original draft, Writing – review & editing. **Martina Chiara Pascuzzi:** Investigation, Writing – original draft. **Elisabetta Di Profio:** Investigation, Writing – original draft. **Antonio Corsello:** Writing – original draft, Writing – review & editing. **Marta Agostinelli:** Investigation, Writing – original draft. **Alice La Mendola:** Investigation, Writing – original draft. **Chiara Milanta:** Investigation, Writing – original draft. **Cristina Campoy:** Methodology. **Valeria Calcaterra:** Methodology, Supervision. **Gianvincenzo Zuccotti:** Methodology; Supervision, Conceptualization. **Elvira Verduci:** Methodology, Writing – review & editing, Supervision, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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