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Review

Recent advances in the field of caloric restriction mimetics and anti-aging molecules

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ABSTRACT

Caloric restriction (CR) mimetics are molecules that produce beneficial effects on health and longevity in model organisms and humans, without the challenges of maintaining a CR diet. Conventional CR mimetics such as metformin, rapamycin and spermidine activate autophagy, leading to recycling of cellular components and improvement of physiological function. We review here novel CR mimetics and anti-aging compounds, such as 4,4′-dimethoxychalcone, fungal polysaccharides, inorganic nitrate, and trientine, highlighting their possible molecular targets and mechanisms of action. The activity of these compounds can be understood within the context of hormesis, a biphasic dose response that involves beneficial effects at low or moderate doses and toxic effects at high doses. The concept of hormesis has widespread implications for the identification of CR mimetics in experimental assays, testing in clinical trials, and use in healthy humans. We also discuss the promises and limitations of CR mimetics and anti-aging molecules for delaying aging and treating chronic diseases.

1. Introduction

Aging is characterized by a gradual decline in organ and body functions, leading to vulnerability to environmental challenges and increasing risks of disease and death (Kirkwood, 2005). While aging is inevitable, recent studies indicate that the rate of aging can be modulated by various factors including diet and lifestyle. For instance, people who consume a plant-based diet that is low in simple sugars and animal proteins show increased longevity compared to individuals who consume a high-caloric, fiber-depleted Western diet (Brandhorst and Longo, 2019; Ekmekcioglu, 2020; Martel et al., 2020a). Similarly, people who regularly perform exercise have a lower mortality risk and better cardiorespiratory and metabolic health status than their sedentary counterparts (Blair et al., 1996; Nocon et al., 2008).

An alternative strategy that delays aging is caloric restriction (CR), which extends the lifespan of various model organisms ranging from yeast to primates (Fontana and Partridge, 2015; Fontana et al., 2010; Mattison et al., 2017). In animal models, CR extends longevity and also improves health markers and reduces the development of major chronic diseases, including cancer, cardiovascular disease, neurodegeneration, obesity and type 2 diabetes (Fontana and Partridge, 2015; Fontana et al., 2010). Many of the beneficial effects of CR in experimental settings may be due to long periods of food abstinence, also called intermittent fasting (de Cabo and Mattson, 2019). Moreover, limiting food intake to a period of 4–12 hours during the day and fasting during the evening and night—a practice also called time-restricted feeding—allows synchronization of physiological functions with the body's circadian rhythm, which may also contribute to the health benefits of intermittent fasting

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(Manoogian and Panda, 2017; Mattson et al., 2014; Zarrinpar et al., 2016).

Anti-aging interventions such as a plant-based diet, exercise, CR, and intermittent fasting can be seen as mild biological stresses that modulate energy- and nutrient-sensing pathways and stress resistance signaling involving adenosine-monophosphate-activated protein kinase (AMPK), mechanistic target of rapamycin (mTOR), nuclear factor erythroid 2-related factor 2 (Nrf2), sirtuin-1 (SIRT-1), foxhead box O (FOXO), and peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) (Calabrese et al., 2012; de Cabo and Mattson, 2019; Lee et al., 2014; Martel et al., 2019; Mattson, 2008). Modulation of these conserved pro-longevity pathways is believed to improve cellular resistance and organ function by activating cellular processes such as autophagy, mitochondrial biogenesis, DNA repair, and expression of antioxidant and detoxifying enzymes. From an evolutionary perspective, organisms that face environmental stress have evolved to shift their limited energy supply away from growth and reproduction and towards maintenance and repair, therefore reducing the rate of aging (Kirkwood, 2005).

Central to these anti-aging interventions is the concept of hormesis, which posits that mild to moderate biological stress produces health benefits, whereas stress of higher intensity can be detrimental (Calabrese and Baldwin, 2001; Calabrese and Mattson, 2017; Calabrese et al., 2012; Mattson, 2008). Accordingly, consumption of phytochemical-rich vegetables or moderate exercise intensity are associated with health benefits, while overconsumption or physical exertion can lead to discomfort, adverse side effects, or even death (Li et al., 2019; Martel et al., 2020a). In addition, intermittent stress is beneficial, whereas chronic stress can be detrimental (Kim et al., 2018). The intensity and frequency of biological stress thus need to be carefully considered to maximize health benefits.

2. Conventional CR mimetics

Given that anti-aging interventions require sustained efforts and discipline, considerable interest has been devoted to identify pharmaceutical compounds or dietary supplements that produce CR-like effects. Various organic compounds have been shown to modulate anti-aging pathways in a manner similar to CR and intermittent fasting (Fig. 1), and are therefore referred to as CR mimetics. Examples of the most studied CR mimetics are acarbose, aspirin, glucosamine, hydroxycitrate, metformin, nicotinamide riboside, rapamycin, resveratrol, and spermidine [see (Ingram and Roth, 2015; Madeo et al., 2019, 2014) for comprehensive reviews].

The best-known CR mimetic is probably rapamycin, a macrolide compound initially isolated from *Streptomyces* bacteria and used to prevent organ transplant rejection due to its immunosuppressive effects. Rapamycin inhibits mTOR, a major regulator of protein synthesis and cell proliferation in response to nutrients and growth hormones (Johnson et al., 2013). Inhibition of mTOR activates autophagy, a cellular recycling process that is believed to rejuvenate cells and mediate the anti-aging effects of rapamycin (Kennedy and Lamming, 2016). Treatment with rapamycin extends lifespan and improves health markers in invertebrates and mice (Johnson et al., 2013). Unfortunately, adverse side effects including increased risks of cataracts, infections and insulin resistance may limit the use of this compound to delay aging in healthy individuals. There is an intensive search for analogous mTOR inhibitors, also called rapalogs, with the hope of finding molecules that have a better safety profile. While first-generation rapalogs such as everolimus and sirolimus have been approved to prevent organ rejection or for cancer treatment, second- and third-generation compounds are currently being investigated in preclinical and clinical studies (e.g., NVP-BEZ235, OSI-027, and RapaLink-1) (Boutouja et al., 2019).

The antidiabetic drug, metformin, is also viewed as a CR mimetic.

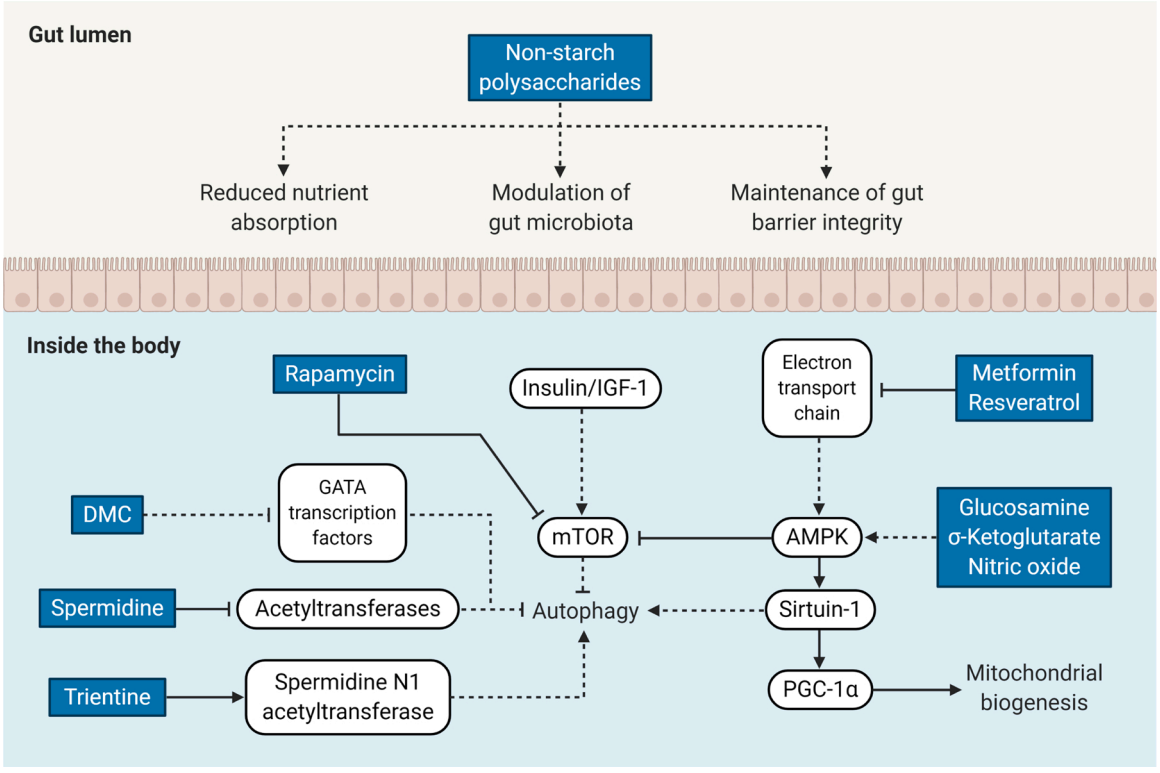

Fig. 1. Mechanisms of action of CR mimetics and anti-aging molecules. Displayed here in blue are endogenous and exogenous molecules that can modulate aging-related pathways in model organisms and the human body. Abbreviations: AMPK, adenosine-monophosphate-activated protein kinase; DMC, 4,4′-dimethoxychalcone; IGF-1, insulin-like growth factor-1; mTOR, mechanistic target of rapamycin; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha. Image created with BioRender.com.

Initially derived from biguanides isolated from French lilac, metformin was shown to improve insulin sensitivity through various mechanisms that include inhibition of complex I of the electron transport chain, activation of AMPK, induced glucagon-like peptide-1 (GLP-1) secretion, and modulation of the gut microbiota (Rena et al., 2017). Due in part to its relatively safe profile and preliminary evidence indicating that it may reduce mortality in humans (Bannister et al., 2014), metformin will be the first CR mimetic to be tested to delay signs of aging and chronic disease in healthy humans as part of the Targeting Aging with Metformin (TAME) clinical trial (Barzilai et al., 2016). However, metformin may also produce adverse side effects, including vitamin B deficiency and cognitive dysfunction in older individuals (Porter et al., 2019), as well as reduced testosterone levels when combined with a hypocaloric diet in obese men (Ozata et al., 2001), possibly leading to erectile dysfunction in some individuals.

Another CR mimetic compound that can block the electron transport chain and activate AMPK is resveratrol (Gledhill et al., 2007), a polyphenol found at low concentrations in red wine, blueberries, raspberries and peanuts. Resveratrol was initially reported to extend the lifespan of yeast, nematodes and fruit flies by activating orthologs of the deacetylase enzyme SIRT-1 (Wood et al., 2004), but later studies showed that it can also interact with a wide range of molecular targets (Pezzuto, 2011), similar to other phytochemicals (Martel et al., 2020a). While resveratrol failed to extend the lifespan of mice fed a standard diet (Miller et al., 2011; Strong et al., 2013), it did prolong the lifespan of high-fat diet-fed mice (Baur et al., 2006), and produced a wide range of health benefits against cardiovascular disease, diabetes and neurological disorders in mice and humans (Baur and Sinclair, 2006; Berman et al., 2017). Synthetic sirtuin-activating compounds (STACs) are being investigated to delay signs of aging and age-related chronic diseases (Dai et al., 2018; Hubbard and Sinclair, 2014). For instance, SRT2104 extended lifespan in mice fed a standard diet, in addition to improving bone mineral density, insulin sensitivity and physical performance (Mercken et al., 2014).

Glucosamine is an amino monosaccharide found in human cartilage and available as an over-the-counter dietary supplement, although inconsistent evidence of its efficacy to improve cartilage has been obtained so far (Ogata et al., 2018; Towheed et al., 2005). Glucosamine extends lifespan in mice by inhibiting glycolysis, activating AMPK, and inducing mitochondrial biogenesis (Weimer et al., 2014). In nematodes, glucosamine also extends lifespan by activating autophagy (Shintani et al., 2018). Perhaps more importantly, several epidemiological studies indicate that people who regularly consume glucosamine have lower all-cause mortality (Bell et al., 2012; Pocobelli et al., 2010) and reduced incidence of lung and colon cancer, compared with non-users (Brasky et al., 2011; Kantor et al., 2018), suggesting possible anti-aging effects in humans.

Spermidine is found in various foods including wheat germ, natto, soybeans, aged cheese, and mushrooms (Madeo et al., 2018). Polyamines such as spermidine and putrescine are endogenous compounds that play an important role in the stabilization of DNA and RNA, modulation of enzyme function, and regulation of protein translation (Madeo et al., 2018). Spermidine extends lifespan in model organisms, an effect that has been attributed to inhibition of acetyltransferases and activation of autophagy (Eisenberg et al., 2016, 2009). While blood levels of polyamines gradually diminish with age (Pucciarelli et al., 2012), supplementation with spermidine or spermidine-rich food appears to replenish levels of this compound and delay aging (Madeo et al., 2018). Accordingly, people who report high intake of spermidine show reduced mortality compared with controls (Kiechl et al., 2018).

Given that the main CR mimetics including metformin, rapamycin, and spermidine can induce autophagy, some authors have proposed that CR mimetics be defined as autophagy activators (Madeo et al., 2014; Mariño et al., 2014). Accordingly, we and others believe that many widely-used pharmaceutical drugs and dietary supplements that possess CR mimetic activities such as aspirin, glucosamine, metformin and statins may produce a wide range of health benefits, at least in part due to their ability to activate autophagy (Ashrafizadeh et al., 2020; Martel et al., 2020a; Pietrocola et al., 2018). Yet, other groups have emphasized that CR mimetics affect a wide variety of cellular and physiological processes that go beyond autophagy (Ingram and Roth, 2015), which may also be the case for some of the CR mimetics identified recently.

3. Mechanisms of action of novel CR mimetics and anti-aging molecules

The flavonoids, chalcones, are found in vegetables and traditional herbal remedies. The compound 4,4'-dimethoxychalcone (DMC) extends the lifespan of yeast, nematodes and fruit flies, in addition to protecting mice against myocardial ischemia (Carmona-Gutierrez et al., 2019). The effects of DMC are due to induced autophagy, but are independent of mTOR and instead involve GATA transcription factors (known for their ability to bind to GATA DNA sequences) which usually inhibit autophagy during aging. Therefore, the mechanism of action of anti-aging compounds such as DMC may differ from that of CR, which relies on reduced mTOR activity (Johnson et al., 2013). Based on these results, the authors proposed that DMC may synergize with other CR mimetics that target mTOR. Notably, DMC has been isolated from a plant traditionally used in traditional Chinese medicine (TCM) to improve longevity (Carmona-Gutierrez et al., 2019).

Ganoderma lucidum, a fungus used for centuries in TCM, is also thought to promote longevity. We reported earlier that high-molecular weight polysaccharides (>300 kDa) isolated from *G. lucidum* reduce obesity, inflammation and insulin resistance in mice fed with a high-fat diet (Chang et al., 2015). The indigestible polysaccharides maintain gut barrier integrity and modulate the gut microbiota, increasing the level of beneficial bacteria such as *Parabacteroides* and *Roseburia*, thereby preventing lipopolysaccharide-induced endotoxemia. Given that signs of gut dysbiosis, leaky gut, and endotoxemia are observed during aging and chronic diseases, including type 2 diabetes, obesity, fatty liver disease and autoimmune conditions (Buford, 2017), fungal polysaccharides would be expected to produce health benefits against various aging-related conditions.

We observed recently that a water extract of *G. lucidum* as well as polysaccharides and oligosaccharides isolated from the extract extend the lifespan of nematodes by inducing autophagy (Peng et al., 2020). The polysaccharides and oligosaccharides also induce autophagy in cultured human cells, suggesting possible conserved effects across species. As noted earlier by other authors (Ingram and Roth, 2015), non-starch polysaccharides represent attractive candidates that could serve as CR mimetics. Accordingly, these polymers may inhibit digestive enzymes, reduce nutrient or bile absorption, and induce the formation of short-chain fatty acids by the gut microbiota, therefore producing various health benefits, while providing only minimal energy (Ingram and Roth, 2015; Martel et al., 2017; Tsujita et al., 2007). Perhaps another indication that these natural polymers function as CR mimetics is the fact that polysaccharide-containing vegetable and mushroom extracts are among the main constituents of the fasting-mimicking diet, which has been shown to reduce signs of aging in animal models and humans (Brandhorst et al., 2015; Cheng et al., 2017; Rangan et al., 2019; Wei et al., 2017).

The synthetic spermidine analog, trientine, stabilizes and activates spermidine N1-acetyltransferase-1 (SAT1), leading to depletion of intracellular acetyl-CoA pools, deacetylation of cytoplasmic proteins, and activation of autophagy (Pietrocola et al., 2020a). While trientine treatment does not affect mouse lifespan, it induces autophagy and reduces weight gain, glucose intolerance, and hepatosteatosis in mice fed with a high-fat diet (Castoldi et al., 2020; Pietrocola et al., 2020a). Trientine has been used as a copper-chelating agent to treat Wilson disease, a rare genetic disorder characterized by excess accumulation of copper in various organs, culminating in liver failure and kidney problems. Notably, it has been suggested that the beneficial effects of

trientine in Wilson disease may be due to activation of autophagy (Pietrocola et al., 2020b). Altogether, trientine possesses CR mimetic activities via activation of the acetyl-CoA-consuming enzyme SAT1, highlighting a new mechanism of action for this CR mimetic.

Alpha-ketoglutarate, an endogenous metabolite of the tricarboxylic acid cycle, extends the lifespan of female mice and improves health markers in both male and female mice (Shahmirzadi et al., 2020). While the mechanism of action of alpha-ketoglutarate still remains obscure, this molecule was found to extend lifespan of fruit flies by activating AMPK and inhibiting mTOR (Su et al., 2019). Of note, alpha-ketoglutarate, a molecule whose levels decline during aging, reduces inflammatory markers and appears to suppress the senescence-associated secretory phenotype (SASP) (Shahmirzadi et al., 2020), indicating that it may be classified as a senomorphic compound (Childs et al., 2017; Martel et al., 2020b). Senomorphics may delay signs of aging by reducing "inflammaging," a chronic, low-level inflammation associated with functional decline in aging individuals (Franceschi et al., 2018, 2017).

Dietary nitrate (NO_3–), found in high amounts in green leafy vegetables and beetroots, has recently emerged as a new possible CR mimetic. Dietary nitrate is converted into nitrite (NO_2–) by bacteria in the mouth; whereas in the stomach, nitrite forms nitric oxide (NO), which can exert local and systemic effects (Lundberg et al., 2018, 2008). While NO is well known for its vasodilatory properties, it can also modulate AMPK and PGC-1α, suggesting that it may produce anti-aging effects (Valerio and Nisoli, 2015). Accordingly, dietary nitrite supplementation extends the lifespan of female fruit flies by reducing the expression of dTOR (the ortholog of mTOR in fruit flies) and upregulating dSir2 (the ortholog of SIRT-1) via the production of NO (Moretti et al., 2020). In addition, polyphenols found in coffee, tea, red wine and cocoa may enhance the conversion of nitrite into NO in the stomach, possibly contributing to anti-aging effects (Rocha et al., 2014). A large number of observations indicate that the beneficial effects of NO occur at low doses, consistent with a hormesis-related mechanism of action (Calabrese, 2001a).

4. Promises and pitfalls of CR mimetics and anti-aging compounds

Arguably the most alluring features of CR mimetics are related to their pleiotropic effects, including the possibility of reducing signs of aging, preventing and treating chronic disease, and perhaps extending lifespan (Madeo et al., 2019, 2014). Short-term clinical studies have shown that CR mimetics can improve specific health markers in humans [reviewed previously in (Madeo et al., 2019)]. The possibility of using CR mimetics to extend lifespan may understandably appear farfetched, but, as mentioned earlier, preliminary evidence from epidemiological surveys suggest that intake of glucosamine, metformin and spermidine is associated with improved longevity (Bannister et al., 2014; Bell et al., 2012; Kiechl et al., 2018; Pocobelli et al., 2010). In the case of spermidine, high blood levels of this compound correlate with longevity in healthy nonagenarians and centenarians (Pucciarelli et al., 2012). Moreover, the difference in mortality risk between the top and bottom third spermidine intake is equivalent to the mortality of a 5.7-year younger age (Kiechl et al., 2018). However, many questions remain regarding the possible effects of CR mimetics on longevity, as well as optimal dose and treatment schedule.

Given that signals regulating cell growth and proliferation pathways (e.g., growth hormone, insulin, insulin-like growth factor-1, IGF-1) and energy- and nutrient-sensing pathways (e.g., AMPK, mTOR, SIRT-1) converge towards the same pathways (Finkel et al., 2007; Martel et al., 2019) (see also Fig. 1), phytochemicals and fungi-derived molecules that have chemopreventive and anti-cancer properties may also behave as CR mimetics. Examples of CR mimetic candidates that modulate longevity-associated pathways include delphinidin, kaempferol, monascin, and myricetin (Martel et al., 2020a). Diets rich in phytochemicals are associated with reduced mortality and cancer, possibly due to the CR mimetic activities of such compounds (i.e., the Mediterranean diet) (Ekmekcioglu, 2020; Martel et al., 2019). In the future, we therefore expect that many new CR mimetics may be discovered in plants and fungi.

Yet, the hormetic effects of CR mimetics can be easily overlooked in cultured cells, animal models and clinical studies due to the wide range of concentrations needed to display hormetic responses, as well as the relatively modest effects observed (usually 30–60 % greater than control) (Calabrese and Blain, 2005; Calabrese et al., 2012). In epidemiological and clinical studies, the genetic background of the host or additional stress produced by lifestyle choices and the environment (e.g., exercise, overeating, poor diet, dietary supplements, and toxins) may reduce or amplify the stress produced by CR mimetics, resulting in absence of effect or even toxicity. For instance, treatment with metformin or high doses of antioxidant vitamins can counteract the beneficial effects of exercise in human subjects (Malin and Braun, 2016; Ristow et al., 2009), indicating that CR mimetics may interfere with lifestyle interventions that modulate anti-aging pathways. Personalization of CR mimetic use may be needed to achieve health benefits.

Another point to consider is that model organisms used to test the activity of CR mimetics, such as nematodes, fruit flies, and mice, have short lifespans and therefore have evolved to develop rapid reproduction mechanisms due to high extrinsic mortality and unfavorable environmental conditions (Kirkwood, 2005). For this reason, short-lived organisms have relatively poor cellular maintenance and repair mechanisms in comparison with humans (Kirkwood, 2005). The benefits of CR mimetics on human lifespan are therefore likely to be more modest than in model organisms. Perhaps CR mimetics may be more useful for reducing the functional decline, signs of aging, and the management of chronic diseases, instead of extending longevity.

CR mimetics act by inducing stress resistance mechanisms, which requires that the capacity to maintain homeostasis in response to stress is intact in the treated organism (Calabrese, 2001b). CR mimetics may therefore be toxic in very old individuals who have reduced homeostasis-regulating capacities (Pomatto and Davies, 2017). Consistent with this possibility, many plant and fungal products extend median or average lifespan in nematodes, but the effects on maximum lifespan are less consistent (Martel et al., 2020c). Moreover, metformin shortened the lifespan of old nematodes (Espada et al., 2020), in contrast to the lifespan-extension effects observed following metformin treatment in young worms (Onken and Driscoll, 2010). Feeding old worms metformin exacerbated aging-associated mitochondrial dysfunctions and led to ATP depletion (Espada et al., 2020), likely due to the failure of old cells to adapt to metformin-induced stress.

5. Conclusions

Conventional CR mimetics like metformin and rapamycin produce robust anti-aging effects in animals and humans. However, these molecules can also generate adverse side effects that may limit their ability to delay signs of aging in healthy individuals. Other endogenous molecules whose levels decline during aging (e.g., spermidine and nitric oxide), as well as CR mimetics that are integral to a healthy diet (e.g., non-starch polysaccharides, polyphenols and other phytochemicals) have better safety profiles and should be considered in future trials. Further studies should also assess the interactions between CR mimetics and other anti-aging interventions like exercise and intermittent fasting. Given the wide range of compounds and targets that can produce CR-like effects, the possibility of identifying new and safe CR mimetics is auspicious.

Declaration of Competing Interest

Y.F.K. is president of Chang Gung Biotechnology Corporation. J.D.Y. is Chairman of the Board of Chang Gung Biotechnology Corporation. J.

M., T.L.H., Y.F.K., J.D.Y. and D.M.O. are named on patents held by Chang Gung Biotechnology and/or Chang Gung University related to the preparation and use of dietary supplements and natural products.

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