REVIEW ARTICLE

Review Article: Potential Molecular Pathway on Herbal Plants for Aging Skeletal Muscle Health

Potensi Herbal terhadap Jalur Molekuler pada Kesehatan Otot Rangka yang Mengalami Penuaan

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ABSTRACT

Sarcopenia is one of the major clinical problems for the elderly and its significant increase number of in expanding research in this area. Precise cellular and molecular mechanism pathway contribution to sarcopenia is still uncertain and involves multifactorial processes such as alteration of physical activity, oxidative stress, nutritional intake, and hormonal changes. There is extensive enormous interest in exploring the potential of herbal supplements to preserve or promote muscle mass in sarcopenia since traditional herbal compounds and formulas are generally cheaper, less toxic and have fewer side effects. This review aims to outline the possible molecular and cellular pathway that may be affected by the herbal and botanical compound. The molecular signaling, pathway involved protein synthesis (IGF-1, PI3-K, Akt, mTOR), muscle regeneration (TGFβ and Myostatin), protein degradation (Ubiquitin-Proteasome System and Autophagy signalling, pathways), inflammation (TNFα and NF-κB) and mitochondrial biogenesis (PGC-1α and AMPK) were identified in this review as potential molecular pathways that affected in vary herbal supplementation. Herbal supplements have shown an ability to affect more than one molecular pathway.

ABSTRAK

Sarkopenia adalah salah satu permasalahan klinik yang penting dan terus meningkat jumlahnya pada lanjut usia. Penelitian terkait dengan mekanisme di tingkat seluler dan biomolekuler semakin banyak dilakukan karena sarkopenia merupakan permalsahan yang kompleks dan dipengaruhi banyak faktor antara lain aktivitas fisik, stres oksidatuf, nutrisi dan perbuahan hormon. Salah satu arah peneltian mengenai sarkopenia adalah pada potensi suplemen herbal untuk membantu memelihara massa otot selama proses penuaan. Hal ini karena herbal dapat bersifat alamiah, lebih murah dan kemungkinan memiliki efek samping yang lebih sedikit. Artikel ini menganalisis beberapa jalur mekanisme yang berpotensi dapat dipengaruhi oleh herbal. Herbal dapat mempengaruhi alur mekanisme tertentu seperti IGF-1, PI3-K, Akt, mTOR, TGFβ, Myostatin, Ubiquitin-Proteasome System, jalur terkait autofagi, TNFα dan NF-κB serta jalur terkait biogenesis mitokondria PGC-1α dan AMPK pada studi yang dilakukan secara in vivo maupun pada manusia. Hal ini memungkinkan eksplorasi lebih lanjut mengenai penggunaan herbal sebagai salah satu strategi pencegahan dan suplementasi pada penurunan massa otot yang disebabkan oleh penuaan.

Introduction

Aging is associated with a progressive decline of muscle mass, quality, and strength, known as sarcopenia (Ali,2014). Precise cellular and molecular mechanism pathway contribution to sarcopenia is still unclear and considered to invol involve multifactorial processes such as alteration of physical activity, oxidative stress, nutritional intake and hormonal changes (Lexell, 1995; Purves-smith, 2014; López-Otín, 2013) 2,3, 4,5 There is some treatment strategy for sarcopenia, such as exercise and herbal supplementation

(Sakuma,2014; Sakuma, 2010; Dhillon, 2017). Since traditional formulated herbal compounds are generally cheaper, less toxic and have fewer side effects than formulated chemical drugs. They are usually applied as alternative medicines in clinical practice to treat many human diseases (Hsiao, 2010; Rondanelli, 2016). A recent review reported some herbal and botanical plants that showed increasing muscle mass in human or animal studies.

This review reveals highlight regarding the possible molecular and cellular pathway that might be affected by the herbal and botanical plants. Given the complexity of the issue, we attempted to elucidate and categorise the cellular and molecular mechanism for prevention and treatment of sarcopenia including the pathway that correlated with stimulation of positive regulators of protein synthesis -
IGF-1 PI3K/Akt/mTOR pathway, muscle regeneration TGF-β and myostatin, mitochondrial biogenesis PGC1 α -AMPK and inhibition of negative regulators such as ubiquitin proteasome system and autophagy signaling pathway and inflammation TNFα- and NFκβ.

Protein synthesis: IGF-1 – PI3-K/Akt/mTOR pathway

GJG is a traditional Japanese herbal medicine containing ten herbal drugs in a fixed proportion. GJG contains several significant components such as paeniflorin *(moutan bark)*, loganin *(Rehmannia root)* and total alkaloids *(processed aconite root)*. A previous study using senescence-accelerated mice (SAMP8) revealed the GJG markedly prevents sarcopenia in 7-week old SAMP8 mice. Administration of GJG to SAMP8 mice maintained the area of muscle fibers in the soleus via normalising signal transduction via IGF-1-Akt axis, inflammation suppression and mitochondrial-related transcription factors. Another interesting finding from this study was soleus muscle comprised more type II skeletal muscle. This finding is may be due to the role of PGC-1alpha that regulates fiber type (Kishida, 2015).

A similar result was also found from a previous *study from Pratiwi (2018) using nutmeg (Myristica fragrans)* extract. Administration of 12 weeks nutmeg extract to 80 weeks Wistar male rats revealed significantly higher gene expression of IGF-1, MyoD and Pax7 in soleus muscle than control. Nutmeg also increases the protein level of Akt, mTOR and muscle mass. Interestingly, this study also identifies potential fiber type shifting from type I to type II in aging soleus muscle. Nutmeg extract has two potential active compounds: macelignan and polyphenols that have already been proven to have PPAR-gamma agonist activity (Lestari, 2019). Another herbal compound is Kamishimotsuto (KST). KST is a supplement containing 13 herbs including Phellodendorn bark, Anemarrhena rhizome and ginseng. Male Sprague-Dwaley rats were received KST (500 mg/kg/d in water) for seven days. Kido et al, 2016 study revealed that KST significantly increased basal p-Akt (Ser473) levels and further augmented resistance exercise-induced muscle protein synthesis through the mammalian target of rapamycin complex1 (mTORC1) signaling pathway. Herbal compound ability to prevent the loss of skeletal muscle function in aged rats was also found from a previous study using an extract of loquat leaf (Erobotrya japonica). Loquat leaf extract administered to young (5-month-old) and aged (18-19-month-old) rats for 35 days revealed increased muscle mass, abrogated age-associated decrease in cross-sectional area and decrease amount of connective tissue in muscle aged rats. The effect of loquat leaf to C2C12 murine myoblast was shown to increase the expression level of satellite cells most likely by activated Akt/mTOR signaling pathway (Sung, 2015).

Muscle Regeneration: Transforming Growth Factor Beta (TGFβ) - Myostatin

Supplementation of catechins *(Camellia sinensis)* significantly effect on muscle strength, follistatin and myostatin in 62 male older adults with sarcopenia. The significantly most notable increase was observed in follistatin, follistatin/myosin ratio, leg press and chest press.

The most remarkable improvement was indicated in the group with a combination treatment of resistance training, and epicatechin supplementation compared with only epicatechin group and control (Mafi,2019).

Another epicatechin study with young (6-month-old) and old (26 months) male mice and followed with quadriceps muscle of human biopsy, showed that consumption of 2 weeks consumption of epicatechin had altered levels of muscle growth modulators and muscle strength (Si, 2019). In mice, myostatin and senescence-associated β-galactosidase levels increase with ageing, while those of follistatin and myogenic factor 5 (Myf5) decrease. Epicatechin also increases handgrip strength and the ratio of plasma follistatin/myostatin (Gutierrez-Salmean, 2014). Another herbal compound that also has good potential is dry roots of *Astragalus membranaceus*, also known as Huang Qi in China. In C2C12 cells in vitro, *Astragalus* is capable of improving insulin sensitivity and decreasing myostatin expression in skeletal muscle through downregulating NF-κB pathway (Liu, 2013). Jaeumganghwa-tang (JGT, *Zi-ying-jiang-huo-tang* in Chinese and *Jin-koka-to* in Japanese) is one of the most widely prescribed traditional herbs in East Asia. Six weeks of JGT administration to young (5-month-olds) and old (19-month-old) male C57BL/6 mice revealed JGT improves muscle strength, increases muscle mass both tibialis anterior and gastrocnemius, decrease muscle damage and suppress protein levels intramuscular TGFβ in aged mice (Lee,2017).

Protein Degradation: Ubiquitin-proteasome system (UPS)

Green tea catechin -EGCG was able to preserve muscle in sarcopenic rats, partly through attenuating protein degradation via UPS1 together with increased expression of anabolic factors. Eight weeks of EGCG administration to 20 month-old Sprague-Dawley rats showed significantly increase gastrocnemius muscle mass, and trend for increased muscle fiber cross-sectional areas compared with aged controls. These increases of muscle mass and muscle-fiber cross-sectional areas associated with significantly lower protein expressions of the intramuscular 19S and 20S proteasome subunits and the Murf1 ubiquitin ligases and also increase of interleukin 15 (IL-15) and IGF-1 (Meador,2015). The nutraceutical properties of sweet chestnut flour extracts were obtained from fruits collected from 7 geographic areas of Tuscany (Italy). These nutraceutical properties have been evaluated in C2C12 myotubes induces to atrophy serum deprivation or dexamethasone. Tocopherol had been identified as counterbalance cell atrophy and the increased muscle atrophy F-box protein (MAFbx)/atrogin-1 expression. This is the first evidence that chestnut sweet has a relevant role in preventing cell degeneration and maintaining skeletal muscle mass (Frati, 2014).

Protein Degradation: Autophagy Signaling-pathway

A previous study using nutmeg extract (Myristica fragrans) identified nutmeg effect to aged soleus muscle in Wistar rats. In this study, soleus muscle in nutmeg group showed increased muscle mass, expression of IGF-1 and satellite cells. Interestingly, the result from this study also reveals that soleus muscle has increased protein level of mTOR and Akt together with the inhibition of autophagy. The autophagy inhibition identified from an increase of p62 and decrease of autophagosome marker LC3BII (Pratiwi, 2018). Furthermore, the exact role of autophagy that crucial in aged skeletal muscle is still unspecified. Chinese herbal medicine, Ginsenoside Rb2, one of the major ginsenosides in Panax ginseng, partly reverses the repression of autophagic pathways involving AMPK or silent information 1 (SIRT1), so the beneficial effect of Rb2 to the fatty liver can be achieved through autophagy induction (Huang, 2017). Another herbal compound that also can upregulated autophagy is resveratrol, Akebia saponin D, Bergamoyt polyphenol fraction, Capsicum annuum extract, licorice and Lycium barbarum (Zang, 2018).

Table 1. Reviewed Articles

No	Herbal	Form-dose	Study subject	Variabel measured	Muscle used	Result
1	Go-sha-jinki-Gan (GJG)	spray-dried, water extracted GJG powder	7-week-old male senescence-accelerated mice (SAMP8)	expression of Akt, GSK-3B, FoxO4, AMPK, PGC1 alpha, MuRF1	soleus muscle (Troponin I for slow muscle, troponin T for fast skeletal muscle)	prevented the progression of sarcopenia in SAMP8 mice by normalizing signal transduction through IGF-1-Akt axis, suppression of inflammation and maintenance of mitochondrial-related transcription (elevated IGF1, normalized level pf Akt phosphorylation, inhibit protein degradation via FoxO)
2	Jaeumganghwa-Tang (JGT) : Angelica gigas, Paenia lactiflora, Rehmania glutinosa, Asparagus cochinchinensis, Atractylodes japonica, Anemarrhea asphodeloides, Phellodendron amurense, Glycyrrhiza uralensis.	dissolved JGT in saline, orally administered of 75 mg/d for 6 weeks	young (5 month old) C57BL/6 mice and old (19-month-old)	Wire hang test	tibialis anterior and gastrocnemius	JGT improve muscle strength, increased muscle mass, reduced expression of TGFB in aged mice
3	Polyphenol curcumin (rhozome Curcuma longa L.)	low dose (50 mg/kgBw/day) and 100 mg/kg-BW/day) curcumin dissolved in dimethyl sulfoxide (DMSO) injected intraperitonially for 28 days	10-week-old male Wistar rats	AMPK phosphorylation, NAD+/NADH ratio, SIRT1 expression and PGC1 alpha deacetylation, cAMP, CREB. LKB-1	gastrocnemius and soleus muscle	combination with eTR increased expression of COX-IV, OXPHOS sub unit, mitochondrial DNA copy number and CS activity
4	Curcumin	0.2% curcumin for 4 months	32 month old male F344xBN rats (three groups :CON, CUR, PAIR)	plantaris muscle strength, Western blot of ..., protein carbonyl, Nrf2, Muscle antioxidant capacity, catalase activity, MnSOD activity	plantaris muscle,	increase Nrf2, no significant difference of protein expression of Catalase, MnSOD, HO-1, TRX/TxNip and activity of catalase, MnSOD, TAC, lower protein carbonyl level, greater skeletal muscle mass,
5	Curcumin	Meriva one tablet/day for 3 months	healthy >65 year old human subjects	hand grip, weight lifting, time/distance before feeling tired after cycling, walkig and climbing stairs, general fitness, proteinuria, oxidative stress, Karnofsky scale, left ventricular ejection fraction		oxidative stress level
6	Apigenin (natural flavobe abundant in various edible plants including celery, chamomil, oranges and grapefruit.	AIN-76A diet with 0.2% and 0.4% apigenin for 7 weeks	5 weeks old male C57BL/6 mice	HE, running distance in treadmill, cell culture, differentiation and siRNA, transfection, immunofluorescent	quadricep muscle	increases skeletal muscle hypertrophy and myogenic differentiation. Induce Prmt7 and PGC1alpha. Apigenin induce Prmt7-p38-MyoD and the Akt-S6K1 pathway
7	Nutmeg Extract	1,8 mg/body weight	80 weeks male Wistar rats	Expression and protein of mTOR and autophagy variable	solues muscle	increases the protein level of Akt, mTOR and muscle mass.

Inflammation : TNFα and NF-κB

Several botanicals *(Phlebodium decamanum, Citrus aurantium, Coffea Arabica, Zingiber officinale, Eugenia punificiola, Panax ginseng, Go-sha-jinki-Gan, Vitis vinifera and Curcuma longa L)* have a significant role in the -prevention of muscle damage induced by inflammation and oxidative stress (Rondanelli, 2016). Resveratrol from *Vitis vinifera* effectively counteracts the TNFα induced muscle protein loss and reverses declining expression of Akt, mTOR, ribosomal protein S6 kinase beta-1 (p70S6K), eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) and FOXO1 but exerts no influence of FOXO3A (Wang, 2014). It demonstrates that resveratrol could represent a possible strategy to improve muscle mass. Another potential botanical that have an impact on these inflammatory pathways in skeletal muscle is curcumin *(Curcuma longa L)*. The early experiment demonstrated that curcumin suppresses activation of NF-κB, induction of heat-shock response, reduction in the expression of *enzyme cyclooxygenase-2* (COX-2) and

promotion of the antioxidant response by activation of the transcription factor.

Mitochondrial Biogenesis: PGC-1α and AMPK

Korean mistletoe *(Viscum album coloratum)* is a semi-parasitic plant that found induced mRNA expression of SREBP-1, PGC-1α and GLUT4 in C2C12 cells and also decreases Atrogin-1 (Jeong, 2017). Administration of 10 weeks curcumin derived from the rhizome *Curcuma longa L* to 10-week-old Wistar rats revealed that curcumin combined with endurance training increased the expression of COXIV, SIRT-1,OXPHOS subunits, mitochondrial DNA copy number, AMPK phosphorylation and PGC-1α deacetylation (Ray, 2015). These findings were supported by the recent study with 32-month-old F344xBN rats administered a diet with 0.2% curcumin for four months. This prolonged curcumin consumption in aged rats showed greater skeletal muscle mass and a more significant presence of NRF-2 nuclear levels. NRF-1 modulates the expression of numerous genes, including those related to antioxidant expression, protein stability and inflammation (Receno, 2019).

Sarcopenia is a complex disorder and involves many possible pathways. Nevertheless, the previous study showed that herbal and botanical compound such as *Camellia sinensis, Curcuma longa and Myristica fragrans* might affect more than one pathway. Furthermore, utilisation of herbal and botanical compound possibly has potential benefit as one of the strategies in sarcopenia prevention and treatment. The balance between protein synthesis and protein degradation is very crucial in sarcopenia. IGF-1-PI3-K/Akt/mTOR pathway most likely become an important pathway that regulates the protein synthesis and inhibit protein degradation through mTOR. There are at least five herbal and botanical compounds have effects in this pathway, such as *Camellia sinensis*, Go-sha-Jinki-Gan, *Myristica fragrans*, Kamishimotsuto and *Erobotrya japonica*. Inhibition myostatin as one of protein synthesis negative regulator also can be affected by a herbal and botanical compound such as Camellia sinensis, Astrogalus membranaceus and Jaeumganghwa-tang.

Meanwhile, some herbal compound that has antioxidant effect may be able to give positive outcome in sarcopenia via PGC-1α and AMPK such as Viscum album and Curcuma longa. In term of UPS and autophagy pathway, although herbal potential in this specific pathway not been explored as many as the other pathway, some of the herbal such as Camellia sinensis, chestnut flour and Myristica fragrans may have a promising result. On the other hand, Vitis vinifera and Curcuma longa also can suppress TNFα and NF-κB as one of the pathways of chronic inflammation during ageing that later has a positive impact on sarcopenia prevention and treatment.

In this summary graphic of the nutraceuticals that have potential affected skeletal muscle health through (Summarry) The balance between protein synthesis and protein degradation is very crucial in sarcopenia. IGF-1-PI3-K/Akt/mTOR pathway most likely become important pathway that regulate the protein synthesis and inhibit protein degradation through mTOR (see Figure 1).

There are at least five herbal and botanical compounds have effects in this pathway, such as *Camellia sinensis,* Go-sha-Jinki-Gan, *Myristica fragrans,* Kamishimotsuto and *Erobotrya japonica*. Inhibition myostatin as one of protein synthesis negative regulator also can be affected by herbal and botanical compound such as Camellia sinensis, *Astrogalus membranaceus* and Jaeumganghwa-tang. Meanwhile some herbal compound that have antioxidant effect may be able to give positive outcome in sarcopenia via PGC-1αand AMPK such as *Viscum album* and *Curcuma longa.* In term of UPS and autophagy pathway, although herbal potential in this specific pathway not been explored as many as the other pathway, some of herbal such as *Camellia sinensis*, chestnut flour and *Myristica fragrans* may have promising result.

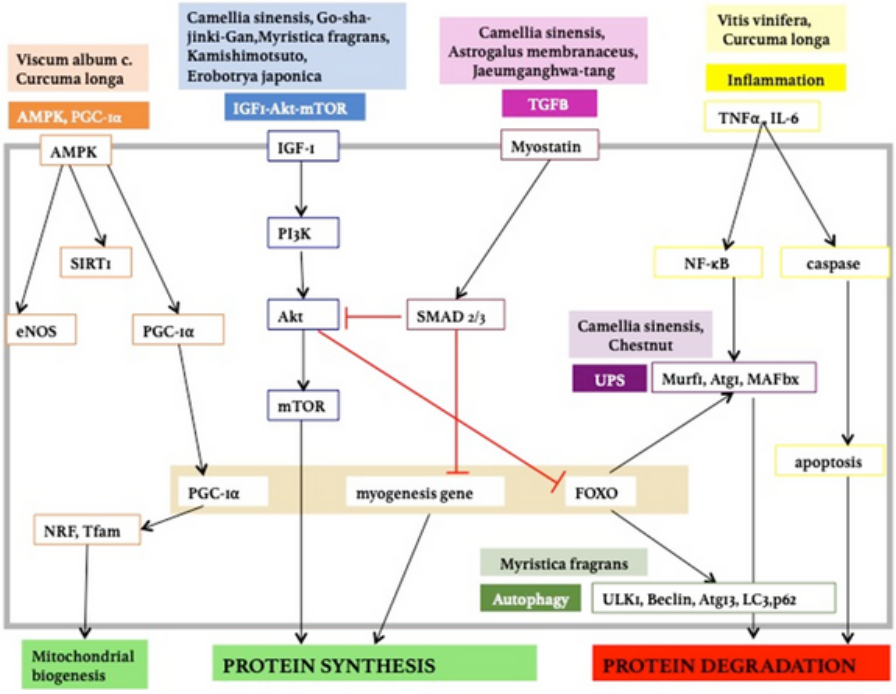

Figure 1.
Herbal and botanical compound and their possible molecular pathway in sarcopenia pathophysiology

On the other hand, Vitis vinifera and Curcuma longa also can supress TNFα and NF-κB as one of the pathway of chronic inflammation during aging that later have positive impact in sarcopenia prevention and treatment.

Conclusions

Although only relatively few human studies have been published on the potential use of herbal and botanical to aged skeletal muscle, the present preview provides highlight information needed to continue efforts to find an effective treatment for sarcopenia.Sarcopenia is very complex and should be approached with multiple pathways. This condition is where herbal supplements have a potential role since some of the herbs in this review shown the ability to give effect more than one molecular pathway safely. The availability result also describes the potential of herbal to become dietary supplementation to prevent loss of skeletal muscle Hence, support for the use of herbal supplements for treatment and prevention of sarcopenia is limited until further research proves their safety and efficacy in humans. Further research will support this herbal and botanical in the future prevention and management of sarcopenia.

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