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Research Article

Metabolomics and Proteomics Approach: Combinatorial Impact of Bioactive Medicinal Plants Based Compounds and Metabolites Affecting Ageing

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Abstract

Background: Ageing is an opening for the initiation of various disorders in an individual's lifespan. It brings degenerative changes in cellular levels which affects fecundity and longevity.

Aim: Here, we reviewed the upcoming advances in metabolomics and proteomics to identify the metabolite and protein network signalling pathways. Along with, the role of various plants metabolites was also reviewed to understand the mechanism behind the anti-ageing activity.

Methods: Clinical studies on ageing provide insight to understand the causative agents through analysing various genetic pathways along with proteomics and metabolomics. In that context, identification of potent biomarkers is required to predict biological as well as chronological age.

Results: In plants, various reports suggest their capability of reversal of degenerative glitches in various signalling pathway. As their metabolites show significant property to cope up with environmental changes along with evolution in specific signalling pathways.

Conclusion: In this review, we can say that plants provide a multitude of bioactive compounds with CNS activity. Along with, the network analyses of ageing or age-related disorders employing proteomics and metabolomics proved to be powerful tool for understanding the core biological processes which influences variations in these abnormalities hindering the longevity of an individual.

Keywords: Anti-ageing; Biomarkers; Proteomics; Metabolomics; Alkaloids; Diterpenes; Phytochemical

Abbreviations: UV: Ultraviolet; 1,5-AG: 1,5-Anhydroglucitol; NAD^+: Nicotinamide Adenine Dinucleotide; $NADP^+$: Nicotinamide Adenine Dinucleotide Phosphate; UDP: Acetylglucosamine-Uridine Diphosphate N-Acetylglucosamine; OA: Opthalamic Acid; GTP: Guanosine Triphosphate; CTP: Cytidine Triphosphate; ADP: Adenosine Diphosphate; IMP: Inosine 5'-Monophosphate; KAT7-$p15^{ink4b}$: Lysine Acetyl Transferase; CUR: Curcumin; LPO: Lipooxygenase; MDA: Malondialdehyde; NO: Nitric Oxide; AGEs: Advanced Glycation Products; APP: Amyloid Precursor Protein; Aβ- Amyloid Beta; p-mTOR: Phospho-Mammalian Target of Rapamycin; p-NF-B: Phospho-Nuclear Factor-Kappa B; D-Gal-D: Galactaose; GOPO: Drug for Joint Supplement; MMP1: Matrix Metalloproteinase; ROS: Reactive Oxygen Species; GB: Gingko Biloba

Introduction

Ageing is one of the inevitable truths of human life's venture. The process of ageing accompanies with decrement in capacity to stabilise body's internal environment and stress handling process [1,2]. Longevity and age-related diseases varied form individual to individual. Cell senescence and oxidative stress are known as major hallmarks of ageing. In this context, another aspect came into the light i.e. Cell senescence. It is caused due to

morphological changes, cell cycle arrest, oxidative stress and chromatin changes [1,3]. The environmental factors and lifestyle of an individual contributes to the ageing process through oxidative modifications of cellular molecules. Due to exposure of oxidative stress the major molecules of cells and lipids got damaged, results in senescence and ageing. The another factor which affects ageing is UV radiations. UV rays instigate the generation of oxidative species which further results in chronic inflammation. Later, disintegration of cell membranes can be referred as photoaging [4,5]. Various reports suggest the phytochemical role for the enhancement of wellness and life span of an individual shown in Figure 1, [6]. In the nature, there are numerous essential components present in plants in the form of fruits and vegetables which are not synthesised by human body but requires in daily basis. There are polyphenols, flavonoids and phenolic components from various herbs and spices that has ability to eradicate free radicals outcome through their antioxidant ability. It was also found that, reduction of antioxidants circulation in the cells showed some association with loss of memory and cognitive impairment. These compounds has capability to stabilise those molecules related to free radicals, lipid peroxidation and radicals produced through UV-radiations [7,8]. Previous reports also associates the declination of ageing process with DNA damage. Furthermore, with the increment of the age is directly linked with genomic instability. To explore the mechanisms elated to DNA damage, genome-wide approaches with various databases provide more insight. To understand the biological aspects in more elaborative way, identification of standardised parameters are required as biomarkers. Through next generation sequencing various individuals with high longevity has been studied to analyse their single nucleotide polymorphism, copy number variations, transcriptomics and epigenomics. Through these techniques, identification of metabolites and potions as biomarkers can be possible for Neurodegenerative Diseases (NSDs). For various NSDs like Alzheimer's disease and Parkinsons disease in them cerebrospinal fluid are mostly taken as biomarker but it always does not provide accuracy in analyses. Thus, in such cases proteomic and metabolomic plays a role to identify relevant biomarkers for example, blood plasma [9]. In this review, we presented the potentiality of metabolomic and proteomic ageing studies from various biomarkers which are responsible for ageing and age-related disorders. Further, we also reviewed the various metabolic pathway for better understanding biological process responsible for ageing. Later, metabolites from various plant has been studied which has capability to combat the causative agents of ageing.

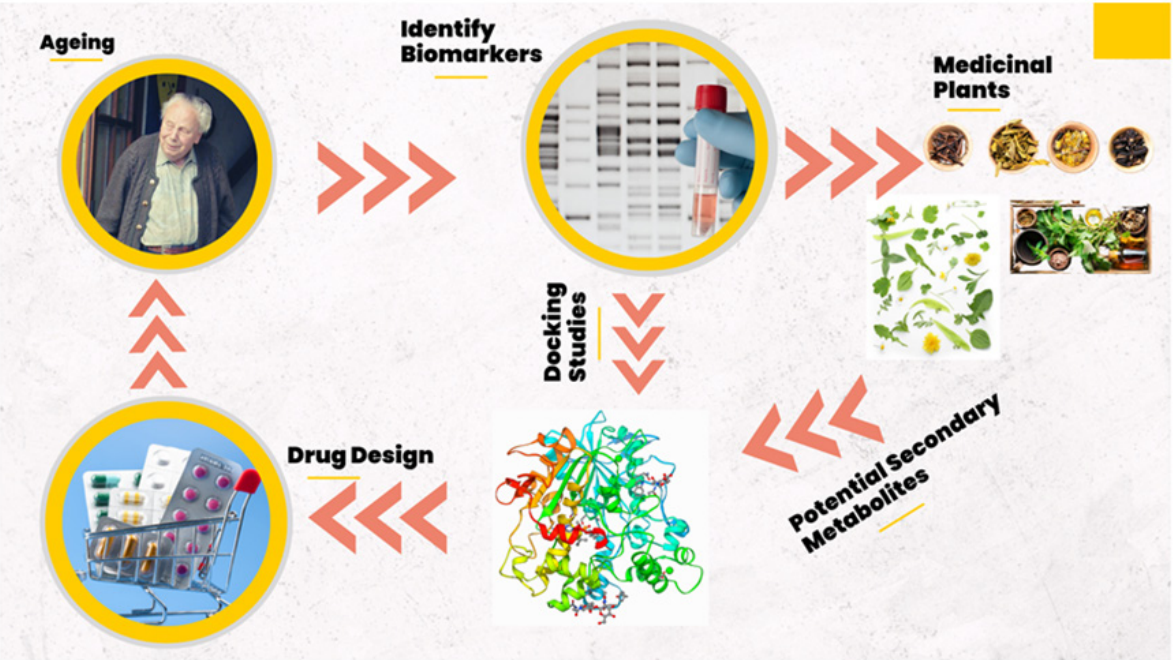

Figure 1: Advanced research pipeline highlighting the procedure to achieve drug required for treating the causative agents related to ageing and age related disorders.

Role of Proteomics and Metabolomics as Biomarkers

Prediction of an individual's chronological age (life lived so far) and biological age (life yet to be lived) could possibly be done through biomarkers. For the quantification, metabolites or proteins can be determined through control diseases individual's samples. In this analysis, the blood samples are very much potent as obsolete biomarkers for age-related disorders [10,11]. In several reports it was noted that due to progression of age, disorders like cancer, stroke, cardiovascular diseases etc., are impede in the aged individuals as compared to the younger individuals [9]. For the better insight, proteomic, metabolomic and genomic technology has been employed to understand the various genetic, metabolite, protein factors responsible for ageing [12].

Enzymes and coenzymes as biomarkers

In the accumulation of studies, it was found that various metabolites like 1,5-Anhydroglucitol (1,5-AG), Nicotinamide Adenine Dinucleotide (NAD^+), Nicotinamide Adenine Dinucleotide Phosphate ($NADP^+$), leucine, isoleucine, UDP-acetylglucosamine etc. shows decrement in their level in elderly people. Usually, 1 deoxy form of glucose (1,5-AG) is present in various foods. It also plays a vital role in oxidative stress defence in body [13]. But during circulation in human body , it got excreted through renal glomeruli and again reabsorbed by renal proximal tubules. In diabetic patients, it was observed that during high blood glucose level they have low 1,5-AG. It is because glucose is competitive inhibitor of reabsorption of 1,5-AG. So, we can consider 1,5-AG as diabetic marker in elderly people. The dipeptides like carnosine and acetyl carnosine has antioxidant capabilities. In muscles and neurons they are found in abundance. The most abundant anti oxidative molecule present in the cell is known as glutathione and Ophthalmic Acid (OA) is tripeptide analog of glutathione synthase to synthesise glutathione. So, we can consider OA as stress marker. For various redox reactions, coenzymes like NAD^+ and $NADP^+$ plays a crucial role. Fo the maintenance of skeletal muscles leucine and isoleucine plays an important role, as they are essential amino acids [14,15].

Components of whole blood as biomarkers

In case of bio-metabolomics, purine and pyrimidines could be considered. These includes GTP, CTP, ADP, IMP, cytidine and adenine. There are also some metabolites which decreases in elderly people but increases during fasting conditions. These metabolites could be taken as biomarkers for ageing. Apart for there other metabolites could be considered as biomarkers are OA, carnosine, leucine isoleucine. In previous reports, it was found that molecule of 2-oxoglutarate oxygenate. This enzyme further demethylate histones and nucleic acids, along with destabilising transcriptional factors. Thus, we can say that fasting is elderly age cause modification of transcriptional networks through genetic or epigenetic level [16,17].

Frailty biomarkers for ageing and cognition

Health risks in advancing age can be easily correlated with frailty. It is caused due to declination of physiological strength of the organs due to onset of the ageing. Despite of loss of strength in organs, cognitive dysfunction, impairment in daily activity are also considered as complex characteristics of frailty. For the detection of physical frailty, multi morbidity, psychosocial aspects, frailty is considered as one of the vital diagnostic tool. Through previous reports it has been noted that 1,5-AG, OA, UDP-glucuronate and creatine showed relativity between cognitive ability and frailty [18-20].

Role of Plants in Anti-Ageing Process

In anti-ageing therapy, plant sourced and nutritional components are considered because this therapy in long term obligations despite of continuation of individual's age. The main objective of the anti-ageing therapy is the alleviating ageing of the stem cells. The study done by Ranbharan et al. found that beta carotene successfully down regulate expression of KAT7 through ectopic expression. KAT7-$p15^{ink4b}$ is newly identified pathway which contributes towards ageing. Here p15 partially off effects of beta carotene results in ectopic expression of KAT7 which up regulates p15 results in mediation of cellular sensitivity [1-21].

Curcuma longa Linn

CUR is a polyphenol found mainly in *Curcuma long* Linn. This ingredient is extensively used in food preparation as colouring agent and preservatives. In previous works, it was observed that CUR acts as epigenetic modulator by enhancing the expression Sirt1 gene at mRNA and protein level. This results in suppression of Histone Acetyltransferase (HAT) and eventually increases the ratio of $NAD^+/NADPH^+$. Through various cellular mechanisms, it has been observed that supplementation of CUR induces cell growth arrest in G2/M phase of cell cycle this results in apoptosis [22]. Furthermore, it also been found that CUR suppresses the molecules related to oxidative stress like , Lipooxygenase (LPO), Malondialdehyde (MDA) and Nitric Oxide (NO). Apart from this, it also chelates molecules which results in the production of Advanced Glycation Products (AGEs). These AGEs are majorly responsible for artery stiffening in elderly age [23]. It was also found that CUR suppresses the molecules which are directly linked with ageing as well as Alzheimer's disease. These molecules are Amyloid Precursor Protein (APP), Aβ (Amyloid Beta), p-mTOR and p-NF--B. It also surpasses the effects of D-gal which is responsible for brain ageing and cognitive impairment. Most importantly for the maintenance of hippocampal area of brain, CUR improves the redox state by inhibition of LPO in brain tissues. This results in increment of potentiality of synapses [24]. Loss-of-function of synaptic mitochondria is also the one of the reason for cognitive disability ageing. In an experimentation in mice model, showed that ingestion of curcumin improves the activity of synaptic mitochondria of hippocampus area by inhibiting inflammation [4-25].

Rosa canina

The secondary metabolites like vitamin C, carotenoids, polyphenols and various flavonoids are present in rose hips (*Rosa canina*). In the plant the galactolipid known as GOPO exhibited strong anti-inflammatory and antioxidant potential which results in synthesis and restoration of collagen [26]. In the ageing process MMP1 (Matrix Metalloproteinase) are responsible for breakdown of collagen and also induces oxidants level in skin. The carotenoid pigment astaxanthin present in rose hip has potential to secure collagen and elastin from Reactive Oxygen Species (ROS) induced by the process of UV oxidative metabolism responsible for ageing [27,28].

Nicotina tobacum Linn

Nicotine is extracted from *Nicotina tobacum.* This metabolite is pyridine alkaloid. It is basically employed from insecticide. But controlled doses of this particular effects attention and memory

of the individual. This is caused due to cholinergic projections to prefrontal cortex binding of receptors present in amygdala and hippocampus. Through meta analysis Heismann et al. found that nicotine consistently enhances the cognitive performances which includes attention, episodic memory and working memory [29,30].

Gingko biloba Linn

Gingko Biloba (GB) is one of the medically important plants for ages. It has biologically active compounds like bilobalide and gingkolides A, B and J from the groups of terpenes. In case of anti-ageing potential GB has ability to regulate platelet activation, enhance NO and provide beneficial effects on peripheral and cerebral blood flow in human brain. Along with, it has potential to modulate various neurotransmitters in neurons. In various studies, it was noted that GB exhibited inhibitory action against monoamine oxidase A, Aβ and hypoxia related issues [31].

Conclusion

The impact of ageing can be seen not only on the basis of clinical research but also in various aspects of entire societies. The mystery of "ageing" is not yet fully solved but we can say that the only on the basis of chronological ageing we cannot decide the entire span of an individual. In this review, its very interesting to understand about few metabolites with their interacting molecules which provides better insight to understand ageing. Along with, the current review on proteomic and metabolic focussing on biomarkers and their networks for better understanding on ageing. Though studies of proteomic and metabolomic networks are in their initial phase and consistent efforts are required to construct consolidate substructure to understand the biological processes in context of ageing and age-related disorders. In this study, amalgamation of various reports presented which provides the beacon of light to understand the value of natural components as therapeutics for various age-related disorders and ageing. Apart from the usage of phytochemical, there are many drug designing or preparing formulation are needed to work on because many of the metabolites are not easily soluble in water, external contamination, shelf life and interaction issues with other supplements are becoming the hindrance in the path. Coalescence of these type of studies would provide us understanding for the functional mechanism which establish correlation between the human immune system, neurodegenerative diseases and role of plant metabolites. Furthermore, we can hope these future efforts would provide quantitative and qualitative assessment of the biomarkers and plant metabolites and its potentiality to across blood barriers in NSDs. Various intriguing minds are working on their fascinating path which is not linear road but apart from all shortcomings remarkable results are expected.

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