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Review: Ageing, Health and Macroalgae

Sunil K. Panchal[1] and Lindsay Brown[2]

[1] School of Science, Western Sydney University, Richmond, NSW 2753, Australia
[2] School of Pharmacy and Medical Sciences, Griffith University, Gold Coast, QLD 4222, Australia

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ABSTRACT

Maintaining health during ageing has become a major public health initiative as the proportion of the world's population aged over 65 years has increased markedly. Macroalgae have been incorporated in the diet for generations, especially in East Asia. Nutritional changes to include macroalgae may provide possibilities for interventions to prevent or reverse the hallmarks of ageing. Their potential to assist in healthy ageing relies on their complex composition including carbohydrates, proteins, minerals, vitamins, fibre and secondary metabolites such as phlorotannins, oxylipins and terpenoids. However, most studies are in animal models with few studies examining the responses in humans to long-term intake. Likely mechanisms of action include reversal of chronic inflammation and gut dysbiosis as part of the changes during ageing. There is now a wide range of foods that incorporate macroalgae, including bread, noodles, yogurt, gluten-free products, and meat and seafood products. Key future priorities with macroalgae include increasing the range of species available for human consumption, defining the health benefits in humans and domestic animals, improving accessibility and decreasing the risk of toxicity from pollutants. Further, health may be improved by indirect effects including wastewater remediation, production of bioenergy and biofertilisers, and decreasing methane production by ruminants. These uses also increase knowledge of macroalgal biology, especially the use of molecular engineering techniques to increase sustainable macroalgal biomass production.

Keywords: Healthy ageing, macroalgae, seaweeds, functional foods, inflammation, gut microbiota

Introduction

Ageing is gradual, individual, predominantly unavoidable and often irreversible with accumulating complex physiological and biochemical changes. Healthy or successful ageing is feasible and so this has become an important challenge due to the increases in the life expectancy and increased elderly population around the world.[1] Ageing is now not only a medical priority, but also a societal and cultural priority.[2] Thus, a holistic approach towards healthy ageing is a plausible way to move forward towards a healthy future of the population. Functional foods have been a focus in the current times to achieve healthy ageing and improve symptoms of chronic diseases.[3] One of the important functional foods in the recent times has been macroalgae or seaweeds.[4-6] Macroalgae contain dietary fibre, bioavailable protein, essential lipids, minerals and vitamins together with bioactive secondary metabolites such as polyphenols.[5] This review will consider the evidence that macroalgae are an appropriate dietary source of sustainable, widely available and lower-cost foods with improved consumer acceptance for people of all ages to prepare future generations for healthy ageing.

Chronic disease in the aging population

Global population increased to 7.89 billion in 2021 with global life expectancy at birth increasing by 22.7 years from 49.0 years to 71.7 years between 1950 and 2021.[7] In Australia, the proportion of the population aged over 65 years doubled from 8.1% in 1950 to 16.2% in 2021[8] while the most common age at death was 87 for males and 91 for females in the decade to 2021.[9] In 2019-2021 in Australia, a 65 year old male could expect to live another 20.3 years; a 65 year old female could expect to live for another 23.0 years.[10] In 2018, the life expectancy for Australians aged 65 years included 9 years disability-free and 11 years with increasing disability for men and 10 and 12 years, respectively, for women.[11] These changes in life expectancy coincide with the development of the WHO focus on the United Nations Decade of Healthy Ageing (2021–2030) to improve the lives of older adults, their families and communities.[12] This action plan includes the Healthy Ageing Collaborative established in September 2022.[13] Worldwide in 2020, the number of people aged 60 years and older was greater than the number of children aged 5 years or less. Further, in 2030, 1.4 billion people are expected to be aged 60 years and more, or about 1 in 6 people.[14] By 2050, the proportion of older adults will be 22% of the world's population with 80% living in low and middle-income countries. Changes in the population of older adults between 2000 and 2019 included increases in both global healthy life expectancy in 200 of 204 countries as well as in years spent in poor health in 198 of these 204 countries.[15] An increase in the ageing workforce may also need extended policies for life-long learning as well as gradual retirement to maintain an acceptable work-life balance.[16] Although the use of chronological age in studies is straightforward and in widespread use, this parameter may not provide an accurate measurement of the extent of human ageing, with possible alternatives including estimates of biological ageing using information such as blood biomarkers,[17] epigenetic age clocks using methylation data[18,19] and physical activity monitors.[20] An intrinsic capacity score together with locomotor, vitality, cognitive, psychological and sensory factors showed strong predictive validity for monitoring ageing trajectories.[21] Providing reliable estimates of biological ageing could result in timely interventions to improve quality and quantity of life for both younger and older adults.

The WHO defines healthy ageing as "the process of developing and maintaining the functional ability that enables wellbeing in older age".[22] Analysis of the concepts and definitions of healthy ageing is necessary to set a clear basis for further studies.[23] Useful evidence-based research to promote healthy ageing requires the use of large databases; 287 cohort studies have been identified but these studies were limited in South America, Africa and the Middle East.[24] Importantly, healthy longevity is changed by social inequalities; as an example, from 2001-2020 in Australia, wealthier, more educated and higher-status individuals showed substantial increases in life expectancy compared with stagnant results in less advantaged groups.[25] Health trajectories in very old adults aged over 85 years are now being studied to determine the biological, social and environmental influences, including nutrition.[26] Treatment of common disorders in older adults may not have well-defined pharmacological therapies, for example, in the treatment of age-associated muscle loss or sarcopenia to increase muscle mass or prevent loss of muscle mass.[27] A related issue is that recommendations for treatment, for example to prevent cardiovascular disease with rehabilitation programmes, should be based on geriatric changes including frailty, comorbidities and cognitive impairment as well as on nutritional status in patients over 75 years of age.[28]

Whether these treatments are aimed to prevent or reverse chronic disease is important; reversal treatments involve individuals with existing healthcare needs in contrast to preventive treatments involving healthy middle-aged to older adults to delay or prevent the onset of ageing-associated changes. Cardiovascular and metabolic disease are major world-wide causes of morbidity and mortality, especially in the ageing population. In 2021, the Global Burden of Disease study estimated that around 529 million people or 6.1% of the world's population were living with diabetes; 96% of those cases were type 2 diabetes.[29] Strategies to reduce the high risk of morbidity and mortality from cardiovascular disease in diabetic individuals should focus on lifestyle management to decrease obesity, followed by pharmacological interventions.[30] The prevalence of obesity was reported as 107.7 million children and 603.7 million adults in 2015.[31] In older adults with cardiovascular disease, diabetes and obesity are associated with structural changes in coronary artery and myocardium, cardiac autonomic neuropathy, endothelial dysfunction, metabolic dysfunction of myocytes and neurons, cardiac adiposity and inflammation.[32] This disease burden underlies the necessity to find effective, sustainable and cost-realistic treatments for diabetes, cardiovascular disease and obesity, especially in the elderly.

Epidemiological studies have identified areas of the world with exceptionally long-lived populations such as the islands of Okinawa in Japan and Ikaria in Greece, referred to as Blue Zones,[33] with low incidence of cardiovascular and metabolic diseases. While Okinawa is defined as a Blue Zone, there are multiple reasons for the increased healthy lifespan including calorie restriction and the composition of the Okinawan diet including root vegetables, soybean-based foods and marine foods such as fish and seaweeds.[34,35] The longevity in the Blue Zones has been used to support the promotion of community-wide dietary approaches to prevent ageing-associated changes to increase healthy ageing, for example, adherence to the Mediterranean diet[36] or to diets using plant-based foods in the elderly population to improve cognition, depression, sensory function, vitality and locomotion.[37] Further, widespread and sustained dietary change from unhealthy to consuming more grains, nuts and fruits and less sugar-sweetened beverages is supported by an increased life expectancy of 10.8 years in males and 10.4 years in females.[38] Widespread acceptance of these diets implies that these diets are examples of healthy nutrition valid for all ageing people, but an alternative view is that it may be more useful to consider these diets as evolving food patterns that have offered benefits to a few specific communities only in recent decades.[33]

The gradual and irreversible process of ageing involves complex molecular and organ changes. Defining these changes offers opportunities for preventive interventions to maintain healthy ageing. The 12 hallmarks of ageing now include two additional parameters, dysbiosis and chronic inflammation,[39] suggesting that nutritional strategies that alter these hallmarks may be important in healthy ageing.[40] The gut microbiome is critically involved in physiological homeostasis, so gut dysbiosis has been associated with a broad range of pathologies. Defining the changes that occur in the gut microbiome, or "microb-aging", is critical to defining the long-term consequences.[41] Chronic conditions that are more common in ageing have been associated with changes in the gut microbiome,[42] such as sarcopenia,[43] impaired cognitive function,[44] frailty[45] and obesity.[46] These associations suggest that healthy ageing can be achieved by interventions that improve the pathological gut microbiome.[47] Although the most logical way to improve the gut microbiome is to develop nutritional strategies, therapeutic success is not guaranteed. As an example, while preclinical studies showed positive responses with nutritional intervention strategies on cognition, clinical studies in humans showed less pronounced effects, depending on age, gender, cognitive decline and basal microbiome composition.[48] Low-grade chronic inflammation or inflammageing is a characteristic of the ageing process leading to cellular senescence, immunosenescence and organ dysfunction.[49] Inflammageing of adipose tissues leads to adipocyte hypertrophy and fibrosis, and contributes to age-related diabetes, cardiovascular disease, cancer[50] and bone diseases.[51] Dietary patterns such as the Mediterranean diet and calorie restriction could decrease the age-related changes in both gut microbiome and inflammageing[52,53] but extensive clinical trials are still required to show that modifying or preventing these hallmarks will produce healthy ageing.

Characteristics of Macroalgae

The terms "marine macroalgae" and the colloquial "seaweeds" lack a formal definition but broadly refer to multicellular marine photosynthetic organisms visible to the naked eye; their characteristics and advantages are given in Table 1.

Table 1: Characteristics and advantages of macroalgae

Plant-like holdfast for anchoring in shallow coastal waters
Divided into green, red or brown; evolution around 1 billion years ago following engulfment of a green or red "cyanobacteria"; genomic analyses defining critical genes for cell adhesion, polarity, communication and differentiation[54]
Freshwater macroalgae such as *Oedogonium* – possible uses for water bioremediation and secondary metabolites as potential biopesticides, plant growth enhancers and potential therapeutic agents[55,56]
Sustainable macroalgal production requires improved propagation and cultivation, solutions to both biotic and abiotic stressors including pests, illnesses and climate change, improved genetic interventions to increase productivity, enhanced technologies to extract products such as biofuels, medicines, nutraceuticals and cosmetics[56,57]
More efficient cultivation techniques than current near-shore techniques including low-cost near-shore farming such as multi-species integrated multi-trophic aquaculture (IMTA) combining seaweed and seafood, together with renewable energy such as wind turbines, land-based macroalgae farming, use of deep sea sites[58-64]
Source of nutrients and bioactive compounds for health benefits[5]

Therapeutic interventions with macroalgae

The potential of macroalgae for healthy ageing relies on their content of carbohydrates, proteins, minerals, vitamins, fibre and secondary metabolites such as phlorotannins, oxylipins and terpenoids.[65] Algae are potential treatments to treat widespread chronic human diseases that are prevalent in ageing providing anti-microbial, anti-coagulant, neuroprotective, anti-carcinogenic, anti-diabetic, anti-obesity, antioxidant and anti-inflammatory responses.[6,66-68] However, most of these proposed therapeutic uses have been tested in animal models rather than in clinical trials in humans which are necessary to characterise the effective doses, and potential therapeutic and adverse responses.[69] This section will examine some examples of compounds present in macroalgae at concentrations that may have therapeutic effects in humans following consumption of whole macroalgae as part of a realistic diet. This list could be broadened by discussing the pharmaceuticals produced by purification of the biomass.

Seaweeds contain complex polysaccharides such as alginates and fucoidans from brown seaweeds, carrageenans and porphyrans from red seaweeds and ulvan in green seaweeds,[70] widely reported as variably representing 5-75% of dry weight. These compounds resist gastric hydrolysis in humans and their breakdown in the colon may increase selected bacteria by the production and metabolic use of short-chain fatty acids (SCFAs). These polysaccharides, often sulphated, may help manage metabolic syndrome by regulating glucose and lipid concentrations and reducing appetite, inflammation and oxidative stress.[71] The *in vitro* anti-inflammatory and immunomodulatory responses to fucoidans have been linked to a wide range of molecular targets to reduce pro-inflammatory molecules and genes but these results are yet to be confirmed in humans.[72] Therapeutic doses in humans have not been defined but may vary widely depending on the source and identity of the edible seaweed.

Macroalgae may present a viable alternative source of long-chain omega-3 fatty acids (EPA and DHA).[73] The anti-inflammatory effects of lipid extracts of seaweeds including omega-3 fatty acids probably involve the down-regulation of pro-inflammatory cytokines and nitric oxide.[74] This anti-inflammatory response may underlie the anti-obesity responses to macroalgae including reduction of *de novo* lipogenesis and increased fatty acid oxidation.[75] Further, seaweed lipids including omega-3 fatty acids may alter the abundance and diversity of the gut microbiome, also altering the gut-brain axis.[76]

Macroalgal proteins are potential dietary sources for healthy ageing to meet the protein demands of older adults as well as providing nutraceuticals to counteract health conditions that are more prevalent in the ageing population. Dietary protein deficiency is widespread as shown by a Global Burden of Disease 2019 estimate of around 147 million cases globally of protein-energy malnutrition leading to about 212,000 deaths annually.[77] Higher protein intakes, particularly from vegetables, improved nutritional status in older adults aged 62-92 years.[78] Macroalgae containing 11-35% protein can provide a sustainable non-animal source of protein without the need of extensive arable land for growing, thus providing an alternative to animal- and plant-based proteins.[79,80] Further, macroalgal proteins can be of high-quality due to their excellent profile of essential amino acids.[81] The only challenge is to overcome the digestibility of macroalgal proteins which can be achieved through the extraction of proteins using various advanced techniques.[79,82,83] Proteins such as lectins from red macroalgae have been tested for antioxidant, anti-microbial and anti-viral, anti-hypertensive, anti-inflammatory, anti-tumour, anti-diabetic and anti-obesity activity.[84] Similar activities have been shown by the green macroalgae, *Undaria pinnatifida*, produced primarily by China, Japan and South Korea containing amino acids, peptides and proteins as well as secondary metabolites, vitamins, fatty acids and sterols.[85]

Macroalgae contain higher concentrations of important essential minerals such as Ca, Cr, I, Fe, Mg, P, Se, Zn, Mn, K and Na than other sources so they could be used to correct mineral deficiency.[86] Care must be taken as intake of seaweeds may exceed recommended intakes of Cr, I and Se, producing negative effects on health.[86] Many seaweeds contain vitamin C, but, as this is not a rich source, seaweeds would only markedly increase vitamin C intake when eaten in large amounts.[87] In contrast, many edible seaweeds including aonori and nori, as well as mushrooms, contain a high proportion of the recommended dietary intake of vitamin B_{12} in a usual dietary intake.[88]

Seaweeds are a potential dietary source of important secondary metabolites with known health benefits such as carotenoids,[89,90] catechins, phlorotannins, flavonols, bromophenols, ferulic acid, vanillin, phloroglucinol, kaempferol, gallic acid, fucoxanthin and quercetin.[91] Many of these components are metabolised by the gut microbiota and gut microbial metabolites are responsible for bioactivity associated with these polyphenols.[91] Phlorotannins such as dieckol, the tridecapeptide IRLIIVLMPILMA, griffithsin, kahalalide F and fucoxanthin are some of the potential secondary metabolites that have been tested in *in vivo* studies and are waiting for extensive clinical trials to quantify effects in humans.[92]

Metabolic syndrome including hypertension, cardiovascular diseases and diabetes is more prevalent in the ageing population.[93] The bioactive compounds in seaweeds have a strong potential to reduce overweight, obesity and diabetes.[69,75] Incorporating macroalgae into the food products can be an effective way of providing valuable bioactive compounds for prevention and treatment of these disorders.[68] The freshwater macroalgae, *Oedogonium*, grown in ash dam water from a coal-fired power station, prevented diet-induced cardiovascular, liver and metabolic changes in rats fed a high-carbohydrate, high-fat diet without changing gastrointestinal histology.[94]

The increase in life expectancy and the emphasis on healthy ageing will stimulate further research on the usefulness of macroalgae to improve health outcomes in the elderly population.[95,96] These therapeutic possibilities will then lead to increased emphasis on the development of functional foods to increase dietary intake of macroalgae.

Macroalgae as functional foods

Although macroalgae have been part of the diet in East Asia for hundreds of years, can they be defined as “functional foods” for healthy ageing? One clear definition is that functional foods given in an adequate dose safely display possible health-enhancing or disease-preventing actions, with examples including probiotics and prebiotics, tea and berries.[97]

We have previously examined the potential of tropical and subtropical foods from Australia, including macroalgae, to be used as functional foods for metabolic syndrome.[98] Functional foods require clinical trials to show therapeutic effectiveness; these trials pose inherent difficulties in the initial organisation and running of the trial and also in the dissemination of new knowledge.[99] One particular challenge with macroalgae trials is the choice of candidate biomarkers for food intake; while phlorotannins and fucoxanthinol may be suitable for brown and red seaweeds, respectively, no candidate marker has been found for green seaweeds.[100] Consumer acceptance is also essential for functional foods.

Increasing research on functional foods in the areas of food, health and technology innovation has led to the definition of five characteristics that measure consumer acceptance of these foods: product, socio-demographic, psychological, behavioural and physical characteristics.[3] Analysis of these characteristics as related to macroalgae as functional foods has not been reported.

Dietary intake of products from seaweeds in Europe and North America is mainly as hydrocolloids such as agar, carrageenans and alginates as thickening and gelling agents in food. In contrast, macroalgae are widely consumed in East Asian countries as raw salads, soups, biscuits, meals and condiments; these seaweed products have been more recently introduced in other countries such as India, Europe, Australia and the Americas, by the Asian diaspora.[101] Increased usage has been promoted by the image that seaweeds are nutritive also adding flavour and texture to the regime, a so-called "gastronomic sensation".[101] As an example, this nutritious image has been used in a Coastal Chef cookbook by 19 Australian chefs [102] as well as in internet sites.[103,104] Traditional and novel food products using the unique properties of macroalgae include bread, noodles, yogurt, gluten-free products and meat and seafood products.[105] Further, customised products with food ingredients including macroalgae can be produced by 3-dimensional digital printing, allowing personalised human nutrition with increased acceptability.[106]

Young Australians are motivated to consume seaweeds by flavour, nutrient content and health benefits but are deterred by poor accessibility, unaffordable pricing and undesirable and non-sustainable packaging.[107] Seaweeds are used to improve the acceptability of meat alternatives, similar to plant- and insect-based products, because these options are considered as healthier and more sustainable.[108] While seaweeds are consumed worldwide, the characterisation of new edible species is an ongoing priority to provide new food products.[109] Concerns remain about an increased seaweed consumption including the exposure to heavy metals, in particular arsenic, increasing the risk of heavy metal toxicity.[109,110] In addition, seaweeds may take up pollutants from seawater, epiphytic bacteria and toxic compounds from algal blooms to cause toxicity in humans.[111] Further, data is limited on the risk of allergic reactions to components of seaweeds such as proteins.[112]

By adding macroalgae to foods, polysaccharides such as alginate, fucoidan, agar and carrageenan, proteins such as phycobiliproteins, carotenoids such as β-carotene and fucoxanthin, phenolic compounds, vitamins and minerals can be included in dietary intakes, thus developing functional foods.[68] Further, due to the presence of these macro- and micro-nutrients, macroalgae can be used in individuals with deficiency of those nutrients. Some of the most common examples of the products developed using macroalgae are cereal-based products such as flour, bread, pasta and biscuits, milk-based products and meat products.[113-115]

Saccharina latissima was liked best as a supplement in bread, and *Saccharina latissima* and *Alaria esculenta* were the preferred species in the spread. *Palmaria palmata* and *Ulva* sp. were also used in this study in bread and spread but the other species were preferred over these two.[116] In another study, fermented *Saccharina latissimi* was used to reduce salt intake due to the content of minerals.[117] Brown macroalgae have been used as food ingredients due to their content of complex polysaccharides, phlorotannins, fucoxanthin and iodine.[118] *Fucus vesiculosus* has been used in fish and fish-derived products whereas *Himanthalia elongata* and *Undaria pinnatifida* have been explored for their functions in meat and meat-based products.[118]

A systematic review of the impacts of macroalgae in various meat products focussed on evaluation of quality, physicochemical and functional properties, sensory characteristics and potential for shelf-life improvement.[114] Addition of macroalgae had minimal effects on pH, protein content and total lipids, while lowering moisture and increasing ash content due to high fibre content, while increasing hardness and chewiness but minimally affecting springiness and cohesiveness.[114]

Many macroalgal compounds can be used in the improvement of food qualities when used as food ingredients. Carotenoids and phlorotannins can be used instead of synthetically obtained antioxidants to help in extension of shelf-life. Carotenoids can contribute towards the colour-enhancing aspect of macroalgae. Proteins, minerals and fatty acids from macroalgae can add nutritional value to the food products.[115]

Indirect effects of macroalgae

Increasing macroalgae production may have indirect effects to improve healthy ageing. The worldwide and acrimonious debate on the role of increasing atmospheric carbon dioxide concentrations has created extensive media coverage. The Intergovernmental Panel on Climate Change report from March 2023 concludes that "all pathways that limit warming to 1.5 degrees C (2.7 degrees F) — with no or limited overshoot — depend on some quantity of carbon removal".[119] This has generated further media coverage on potential removal strategies including expanding macroalgae production.[120] Modelling of ocean-based carbon removal by open-ocean mariculture in the surface layer and fast sinking to the deep seafloor showed reduction of atmospheric and terrestrial carbon reservoirs but with substantial effects on marine ecosystems and biogeochemistry with reorganisation of food webs in the oceans.[121] Increasing carbon removal by macroalgae will require decarbonising of supply chains, use of long-term carbon reservoirs, expanding farming outside traditional cultivation areas and developing robust models to trace seaweed carbon.[122] In addition, higher global temperatures will change the metabolic profile of macroalgae, for example increasing amino acid concentrations.[123] Increasing production of seaweed biomass has a wide variety of roles that may support healthy ageing, including wastewater remediation and production of bioplastics[124], bioethanol[125], biofuels[126] and biofertilisers[127]. Further, the red macroalga *Asparagopsis taxiformis* and *Asparagopsis armata* markedly reduced enteric production of the greenhouse gas, methane, by ruminants.[128] Metabolic engineering techniques are now being developed to further increase macroalgal biomass production.[129] Increased production of macroalgae for these products will stimulate research into macroalgae and increase commercial support for efficient macroalgae production of nutraceuticals and foods for healthy ageing.

Conclusion

The proportion of the ageing population has increased markedly over the last 50 years, as has the knowledge of the chronic changes that occur during ageing. Further, the options have widened for treatment of the chronic diseases that are more common during ageing. Despite this increase in options, healthy ageing remains a goal rather than an obvious outcome. The use of functional foods has now become part of the community discussion of pathways to health. Macroalgae (seaweeds) have been included in this discussion but there are major barriers to a widespread acceptance of macroalgae for health. Macroalgal biology is increasing on a rapid trajectory but from a low base. Most macroalgal species have not been characterised, optimal growing conditions at commercial scale are still being developed, isolation of commercial quantities of the active ingredients has rarely been achieved, and the clinical trials that are needed to support large-scale and long-term therapeutic uses of macroalgae or their components are rare. Of particular relevance to this review, most studies on potential health benefits are in animal models of human diseases. In contrast, clinical trials aimed to quantify health benefits in human adults or to reverse ageing-related diseases in elderly humans using macroalgae or their components have only rarely been published. Further, clinical trials to prevent chronic ageing-related disease by preventive treatment in healthy young or middle-aged adults are urgently needed.

The valid aim of extending healthy ageing remains a goal but the procedures already exist to make this aim a reality. Key future priorities with macroalgae include increasing the range of species available for human consumption, defining the health benefits in humans at all ages and domestic animals, improving accessibility and consumer acceptance, and decreasing the risk of toxicity from pollutants. Likely mechanisms of action include reversal of chronic inflammation and gut dysbiosis as part of the changes during ageing but these mechanisms need to be refined and extended. There is now a widening range of foods that incorporate macroalgae from basic foods such as breads and noodles to gourmet restaurant meals. Further, health at all ages may be improved by indirect effects of macroalgae including wastewater remediation, production of bioenergy and biofertilisers, and decreasing methane production by ruminants. These non-nutritional uses also increase knowledge of macroalgal biology as part of the process of improving productivity and commercialisation of these processes.

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