Alzheimer's Disease & Treatment

Chapter 4

Fruit Fly (*Drosophila melanogaster*): A Viable Model for Screening Tropical Functional Foods for Neuroprotective Properties

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Abstract

In the prevention of chronic disease such as neurodegenerative diseases, nutrition is critical; not just to meet nutritional requirements but more importantly to contribute to the total wellness of the consumer by either preventing and/or managing such disease conditions. This has further promoted the concept of functional foods and nutraceuticals. However, while several studies abound on the huge abundance and diversity of functional foods especially in tropical parts of the world, there is a still serious limitation to rapid and high throughput experimental screening for neuroprotective properties of several functional foods especially in developing nations. These limitations include modern, effective and accessible experimental models for rapid screening, cost of research and ethical issues with animal use among others. Fruit fly (*Drosophila melanogaster*) has emerged as a very useful model of neurodegenerative disease and could be more effective for therapeutic screening for neuroprotective properties of functional food and nutraceuticals especially from developing countries of tropical Africa. This

model organism has such advantages as short life span, high fecundity, low cost of maintenance, ease of handling and small genome size already sequenced and easy to manipulate. Therefore, this chapter review recent trends in functional food research especially of tropical African origin and how *D. melanogaster* can help optimize the effective screening of their neuroprotective properties.

1. Introduction

The saying "Let food be thy medicine and medicine be thy food" of Hippocrates about 2,500 year ago has attracted much scientific attention. This is clearly seen in the interest shown by scientists from various relevant fields in the role of specific food in enhancing health and well- being. While all foods could be said to have functionality mainly in terms of their nutritive values, however, the idea of functional food is not to be viewed as only necessary for living but is to also contribute to the total wellness of the consumer which involves prevention and reduction of disease risk factors, thereby enhancing the overall physiological function. In 1989, Stephen DeFelice, MD, (founder and chairman of the Foundation for Innovation in Medicine (FIM), Cranford) coined the word 'nutraceutical' from nutrition and pharmaceutical [1]. Nutraceutical can be described as a food (or part of a food) that provides medical or health benefits including the prevention and or treatment of a diseases. Nutraceuticals are often said to be products that are extracted or purified from animal, plant or marine sources which have shown physiological benefit or known to protect against chronic diseases.

Neurodegenerative diseases are pathologies with many ethology. Studies have shown that impairments in neurochemistry, oxidative stress and elevated metal ions deposits in the brain are few of the factors that contribute to the progression of neurodegenerative disease [2]. In order to set the key etiological factors as a focal point, it is very important to develop a multidimensional therapy that will prevent and manage these diseases. Most drugs designed all have short live span and side effects [3]. In order to overcome this limitation, dietary interventions as a complementary approach in management/prevention of neurodegenerative disease becomes imperative for holistic management.

Many studies have been published on therapeutic properties of functional foods especially of tropical African origins. In the last few decades, many interesting research publications have originated from Africa on therapeutic properties of several tropical functional foods. However, one major limitation to full evolution of functional food research in Africa has been adequate screening models. Many of published data on functional food from Africa has been from *in vitro* research with a good number on *in vivo* animal (usually mouse and rats) models. However, the current advocacy on ethical controls on laboratory rodent use is gradually challenging biomedical research generally in Africa. Therefore, it has become imperative to explore alternative models. *Drosophila melanogaster* also called fruit fly has emerged to the fore when it comes to therapeutic screening of functional foods, nutraceuticals, chemotherapeutic drugs

and lots more. Screening a large pool of therapeutics in search of few lead compounds is cost effective using Drosophila.

2. Functional Foods and Nutraceuticals: An Overview

The term functional foods originates from Japan in the mid-1980s and it often referred to processed foods that possess active ingredients that aids specific function in the body in addition to its nutritional values. Around the world, Japan is foremost in creating specific regulatory approval process for functional foods. Functional food possesses a wide range of definition, one of which was published in European consensus publication as: "a food is said to be functional if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond its adequate nutritional effects, in a way which is relevant to either the state of well-being and health or the reduction of the risk of disease". Another definition is given by the Institute of Medicine of the National Academy of Sciences "as any food or food ingredient that may provide health benefit beyond the traditional nutrients it contains" [4]. Another simpler definition states that functional food are foods that are similar in appearance to conventional food and are often regarded as normal diet, but have been modified to provide physiological benefits apart from the basic nutrients they provide [5].

Functional food and conventional foods are often similar in appearance or even closely related. But they differ slightly in that functional foods has physiological benefits and are capable of reducing of the risk of chronic diseases beyond provision of nutritional values [6]. Functional food components are potentially beneficial components present in naturally occurring foods or functional ingredients added. These components include carotenoids, dietary fibres, fatty acids, flavonoids, phenolics acids, plant sterol, prebiotics and probiotics, soy proteins, vitamins and minerals, isothiocyanates. The concept of functional food and nutraceuticals are often used interchangeably but they can be distinguished. Functional food is a broad term used to describe food or part of food with specific function [7], whereas nutraceuticals deals with the expected result of the products which could be prevention or treatment of diseases. While functional food can also be food products that are required to be taken as part of usual diet so as to elicit beneficial effect (therapeutic effect) that goes beyond the known traditional nutritional benefit [8], nutraceuticals on the other hand could be described as purified products from plant or animal functional foods.

3. Functional Foods are Beyond Nutrient Sources

A lot of scientific findings have proven that functional foods possess a wide range of therapeutic potential in the prevention and management of several diseases afflicting humans. Since functional food is mostly of plant origin the bioactive components present therein are majorly phytochemicals. These includes phenolic acids, flavonoids, alkaloids, ascorbic acids and vitamin E. These components have been reported upon to possess antioxidant property

which is one of the proposed mechanism through which they bring forth their therapeutic effects [9]. Antioxidants are essential molecules which are needed to counteract the deleterious effect caused by free radicals in biological tissues. Although, every biological organism has endogenous antioxidant systems to effectively manage the oxidative damages of free radicals, an overwhelming amount of free radicals could cause a tilt in this check and balance system which could lead to extensive tissue damage; this phenomenon is called oxidative stress. Oxidative stress often necessitates sourcing antioxidants from exogenous sources such as found in functional food. Furthermore, oxidative stress has been linked to the pathogenesis and progression of many human diseases such as diabetes, cardiovascular disease, inflammation, cancer and dementia among others. Interestingly, reports have shown potentials in the management of these diseases such as ginger and turmeric for the management of hypertension [10,11], green leafy vegetables for the management of dementia [12,13] and legume seeds for the management of type 2 diabetes [14,15]. The health benefits of fruits and vegetables in preventing chronic diseases including type 2 diabetes are attributed to their antioxidant constituents including polyphenols, carotenoids and ascorbic acid which could help prevent or ameliorate oxidative stress [16]. In addition to ameliorating oxidative stress, the bioactive component of fruits and vegetables can elicit their antidiabetic effect by stimulating insulin secretion and inhibiting carbohydrate absorption in the small intestine ultimately resulting in lower blood glucose level [17, 18]. In the past decades, fruits and vegetables have gained much interest in the management of cancer [19]. Although, most functional foods are of plant sources but some are also of animal origin that is quite interesting. Examples of such are (n-3) fatty acids from fish and conjugated linolenic acid present in milk and meat products [20]. In the management of cardiovascular disease, (n-3) fatty acid which are essential class polyunsaturated fatty acids have shown potential.

4. Tropical Functional Foods for the Brain

Functional foods that have neuroprotective properties are of higher focus due to the increased incidence of neurodegenerative diseases. A brief outline of research findings on some tropical functional foods with neuroprotective properties is given in table 1. Nevertheless, it is still clear that many outstanding *in vitro* findings do not often get to *in vivo* levels due to among others factors of cost and ethical issues with the use of mammalian models.

Table1: A brief outline of research findings on some tropical functional foods with neuroprotective properties

Class	Common name	Botanical name	Plant part	Major findings	Nature of study	Reference
Fruits and nuts	Citrus (orange, grape fruit and shaddock)	*Citrus spp.*	Peel	1. AChE, BChE and MAO inhibitory properties 2. Antioxidant properties	*In vitro*	[21]
	African star apple	*Chrysophyllum albidum*	Fruit			[22]
	Mangosteen	*Garcinia mangostana* Linn.	Fruit	1. Antioxidant properties 2. Protect against H_2O_2-induced oxidative stress in NG 108-15 neuroblatoma cells.	*In vitro*	[23]
Spices	Tumeric	*Curcuma longa*	Rhizome	1. Chronic dietary inclusion of turmeric rhizome protects against MPTP-induced PD in mice 2. Dietary inclusion of turmeric rhizome ameliorates alterations in activities of major neuronal enzymes in synaptosomes from the cerebral cortex of hypertensive rats	*In vivo*	[24, 25]
			Curcumin isolated from turmeric rhizome	1. Protect against ethanol-induced brain damage in rats 2. Protects blood-brain barrier integrity in cerebral ischemic rats 3.Synergize antiamnesic and anticholinesterase properties of Donepezil in rats	*In vivo*	[26, 27]
	Pepper	*Capsicum* spp.	Fruit	1. AChE and BChE inhibitory properties 2. Antioxidant properties	*In vitro*	[28, 29]
				Ameliorate cyclophosphamide induced oxidative stress in rat brain	*In vivo*	[30]
			Capsaicin isolated from red pepper	Ameliorate biochemical markers in MPTP-induced PD in male C57BL/6J mice	*In vivo*	[31]

	Ginger	*Zingiber officinale* Roscoe	Rhizome	Enhance cognitive function and protect against neurochemical alterations in experimentally induced mammalian models of cognitive dysfunction	*In vivo*	[32]
			Essential oil	Prevents oxotremorine-inducedtremors and increased the latency of pilocarpine-induced seizures, as well as survival at 50 and 100 mg/kg in male swiss mice. However, higher dose of 100 mg/kg presents some cognitive impairments		[33]
	Onion	*Allium cepa*	Bulb	Attenuation of ischemia-induced oedema and elevation in MDA level in mice brain	*In vivo*	[34]
				Protection against ischemic neuronal damage in Gerbil hippocampus		[35]
Vegetable	Tomato	(*Lycopersicon esculentum* Mill. var. *Esculentum*	Fruit	1. AChE inhibitory property 2. Inhibit Fe^{2+} and QA-induced lipid peroxidation in rat brain	*In vitro*	[36]
		Lycopersicon esculentum Mill. var. *Cerasiforme*)				
	African Jointfir	*Gnetum africanum*	Green leafy vegetable	AChE, BChE and MAO inhibitory properties	*In vitro*	[37]
	Fluted pumpkin	*Telfairia occidentalis*)	Green leafy vegetable	1. AChE inhibitory property 2. Inhibit Fe^{2+} SNP and QA-induced lipid peroxidation in rat brain	*In vitro*	[12]
	Bitter leaf	*Vernonia amygdalina*	Green leafy vegetable	Antioxidant properties and Inhibit H_2O_2-induced lipid peroxidation in rat brain	*In vitro*	[38]
	Horseradish	*Moringa oleifera*	Green leafy vegetable	Ameliorate cognitive dysfunction in STZ-treated rats treated with acarbose	*In vivo*	[39]
	Black nightshade	*Solanum nigrum* L	Green leafy vegetable	Ameliorate cognitive dysfunction and neurochemical impairments in scopolamine-treated rats	*In vivo*	[13]
	African eggplant	*Solanum macrocarpon* L		AChE inhibitory and antioxidant properties	*In vitro*	[40]

AChE= Acetylcholinesterase. BChE= Butyrylcholinesterase, MAO=Monoamine oxidase, MDA=Malondialdehyde, MPRP=1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, PD= Parkinsons's disease, QA= Quinonilic acid, SNP= Sodium nitroprusside, STZ= Sterptozotocin

5. Fruit Fly (*Drosophila Melanogaster*) as a Therapeutic Screening Model for Functional Foods

5.1. Life cycle of *drosophila melanogaster* in brief

Drosophila has a very speedy life cycle **(Figure 1).** A single mating pair that is fertile can produce hundreds of offspring that are similar genetically in a period of 10- 12 days at room temperature. This is highly contrasting to the laboratory rodents that produce just a few offspring every 3- 4 months. The development of this fly occurs in stages (complete metamorphosis): the egg (embryo), larva, pupae and the full grown adult. The larva stage is actually in three phases; the first instar larva, second instar larva and the third instar larva. The third instar larva often wander in the culture media and it is at this phase the pupa develops. A great morphological changes often characterize the development of the third instar larva into pupae and eventually to the full grown adult. Under optimal condition life span of an adult fly is approximately 120 days. (For further reading, see Abolaji et al., [41] for more detailed review on drosophila development and husbandry).

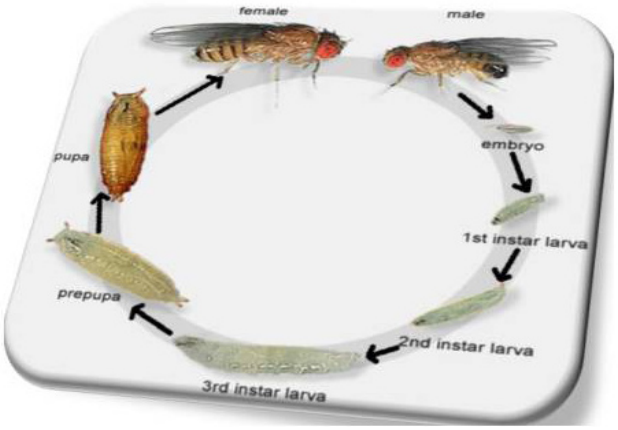

Figure 1: Life cycle of fruit fly (*Drosophila melanogaster*) (Abolaji et al., [42])

5.2. Potentials of *Drosophila melanogaster* as Model Organism

As stated earlier, functional food and nutraceuticals are of great interest to humans. Therefore, it becomes imperative to screen large pool of potential sources of functional foods and nutraceuticals for their perceived therapeutic functions; obviously, using humans as a screening model will be ambiguous, the extreme number of rats to be used will be unethical and *in vitro* studies will be insufficient. In search of a way out, the use of *Drosophila melanogaster* as a model animal comes to fore. Although, it might seem ironic that a 'tiny' fruit fly serving as a model for human therapeutic screening and physiologically spealing, there exist a wide range of differences between humans and the fruit fly. However, there is genetic homology between them which is the striking factor that makes research using *D. melanogaster* unique. Approximately 75% of diseases causing genes in human are conserved in *D. melanogaster* [43]. Another striking fact about *D. melanogaster* is the ease and cost effectiveness to manipulate and create a transgenic fly using high throughput genetic procedures [44]. With the availability

of these procedures, it is easier to generate models of human disease rapidly through various genetic engineering processes including mutation, genetic inactivation, or mis-expression of fly homologs of human disease genes and protein themselves.

Drosophila can also be used to monitor various pathological indices of neurodegeneration (figure 2). The wide varieties of these indices spanning biochemical, anatomical, molecular and behavioural aspects of neurodegeneration makes this organism quite useful as a research model. The flies present several anatomical features that can be monitored as indices of incidence and progression of neurodegeneration. Such features as simple as wing shape, eye colour and shape, fly size, larva size, and as complex as neuronal integrity, microtubule formation, synaptic formation and function could be used as markers of neurodegeneration as well as to monitor the potentials of any test therapeutic agent [45-48]. Such intrinsic anatomical alterations are often the phenotypic realities of several biochemical and molecular changes which ultimately reflect in their behavioural patterns such as their ability to climb (negative geotaxis), sleep-wake behaviour (circadian rhythm), copulation (aggressive behaviour) and their spatial orientation (movement pattern). Usually, fly models of neurodegeneration with marked anatomical and behavioural changes display concomitant biochemical and molecular modulations such as elevated level of reactive oxygen and nitrogen species, impaired cholinesterase activity, alterations in activities of antioxidant enzymes and levels of neurotransmitters, as well as modulation of gene expression levels of proteins of therapeutic importance; all these offers several useful points of evaluating therapeutic potentials of test compounds [46, 49-54]. Furthermore, the short and completely sequenced genome, coupled with the availability of relevant and accessible bioinformatics tools for Drosophila such as 'fly base' (http://flybase.org) makes investigations using Drosophila as model organism at the molecular level more achievable and attractive.

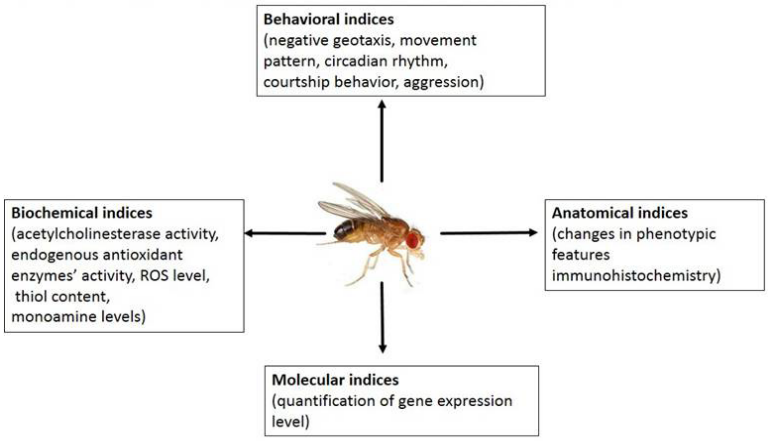

Figure 2: Chart showing the various pathological indices that *Drosophila melanogaster* can be used to monitor.

5.3. Current Possibilities

While the use of *D. melanogaster* for biomedical research in general and functional food research in particular in developing parts of the world such as Africa is still at its nascent

stage, it is interesting to note that a few interesting findings are already being published. One of such study accessed the toxicological implications of the popular condiment-monosodium glutamate and reported the toxicological implications of its consumption [55]. In this study, the author reported that feeding flies with monosodium glutamate up to 2.5 g/kg diet for five days significantly reduced their longevity, induced production of reactive oxygen and nitrogen species, hydrogen peroxide production and impaired activities of catalase and glutathione-S transferase antioxidant enzymes. Another study by Farombi et al., [56] recently used *D. melanogaster* as a model organism to show the ameliorative effect of kolaviron (the biflavonoid from bitter kola) on rotenone-induced toxicity. The biflavonoid was able to ameliorate the impaired locomotor performance, reduced life span, altered enzymes' activities and ROS/RONS production induced by rotenone. Another biflavonoid (hesperidin), a nutraceutical from citrus has been investigated for its therapeutic properties using *D. melanogaster* as model organism [57, 58,54]. Furthermore, curcumin which is adjudged the main polyphenol in turmeric was also shown to modulate acetylcholine gene expression level in *D. melanogaster* [53]; in this study, the authors reported that curcumin-supplemented diet improves survival ability increased antioxidant enzymes' activities but decreased AChE activities. The mRNA expression levels of AChE was similarly supressed; the authors proposed this as one of the major mechanism behind the neuroprotective properties of this compound as previously reported [59-62]. Just recently, Abolaji et al., [63] studied the ameliorative effect of resveratrol on oxidative damage induced by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) in *D. melanogaster*. MPTP has been extensive used to model Parkinson's disease in various animal models and as noted by the authors, this was the first time MPTP-induced toxicity will be studied in drosophila. These few are a testament to the possibilities of using *D. melanogaster* for functional food research especially in developing world. (For further reading, see 'Notes on Recent History of Neuroscience in Africa', by Russell, [64])

5.4. Limitations

Although fly models can have high degrees of conservation and validity, providing opportunity for rapid screening and interpretation of results, however, modelling multifactorial human disease may be a bit complicated mainly due to the fact that such fly models usually express only certain aspects of the disease, making result interpretation more complex. Furthermore, while there seems to be a strong correlation of toxicity between the two organisms, nevertheless, due to metabolic differences, it is possible to observe that some drugs toxic to flies might not be in humans and vice versa [65]. In view of these limitations, it should be emphasized that D. melanogaster could be a useful model for rapid screening of a pool of functional foods and isolated nutraceuticals, as well as post screening validations to narrow down potential therapeutic candidates to a much smaller pool of lead substances/compounds, which could still be necessary to validate using conventional mammalian experimental

procedures. Nevertheless, with increasing attention being given to the use of *D. melanogaster* for biomedical research globally, which is attracting more sophisticated experimental protocols and re-validated research findings, these limitations might soon be overcome and a 'fly-to-bed' research approach, allowing direct clinical trials of validated fly-based research findings might not be too far away.

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