# MITOCHONDRIA IN CHINESE MEDICINE
## Part 1: Mitochondria and Adaptation

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Mitochondria have been of paramount importance to cell biology since being discovered to be the site of cellular respiration, and gained a certain notoriety when the byproducts of this process, known as free radicals or reactive oxygen species (ROS), were identified to be behind many disease processes. In recent years researchers have discovered that, not only is the delicate balance between energy and ROS maintained by mitochondria far more complex than previously thought, but they are also involved in biosynthesis, immune modulation, cellular signalling, adaptation to stress, responses to drugs including herbs, thermoregulation, circadian rhythms, cellular differentiation, ageing and programmed cell death. This has shifted the perspective of researchers on mitochondria from being simple energetic factories and polluters of our internal environment, to key determiners of biological fate.

I have spent the last 4.5 years studying for a PhD into the effect of herbs on mitochondria and how we might use this to solve some age-old problems in the herbal medicine industry. In this series of four articles I want to share some of the things I have discovered, starting with an introduction to the many roles mitochondria play in regulating our bodies and how these might be relevant to Chinese medical practices in general, followed by a discussion of antioxidants and their role in the Chinese pharmacopoeia, a similar review of adaptogens, and finally a summary of my own research into how mitochondrial functional analysis might be useful in determining the quality and potency of herbal medicines.

### Respiration

The most established role of mitochondria is that of respiration. This is the process whereby fatty acids and sugars obtained from our diet are transformed into chemical energy that the body can use as fuel for most of its biological processes. It does this by attaching a phosphate molecule with a high energy bond to adenosine diphosphate (ADP) to form adenosine triphosphate (ATP). This can then be detached and returned to ADP with the released energy utilised when needed.

All cells are able to respire through the process of glycolysis, which yields two molecules of ATP for every molecule of glucose, but mitochondria are capable of using the byproducts of this process along with fatty acids and oxygen to produce another ~30 ATP through a process known as oxidative phosphorylation. In this process, electrons are transferred through the electron transport chain, which provides the energy to pump protons across the inner membrane of the mitochondria resulting in an electrochemical gradient that drives the enzyme ATP synthase to generate large quantities of ATP. This process can only take place in the presence of oxygen which is required to receive the electrons and protons at the end of the chain making water ($H_2O$). This extraordinary efficiency of energy production has enabled cells to meet the energy requirements necessary for complex organisms to develop, giving rise to the incredible diversity of life on earth (Callier, 2022).

### Reactive Oxygen Species

No process of generating energy is perfectly efficient and this applies to the electron transport chain too.

An estimated 0.2-2% of the electrons in the chain leak where, without their proton counterpart, they attach to oxygen to form superoxide, a highly reactive molecule that can easily damage the mitochondria and other cellular components (Zhao et al., 2019). In order to protect itself, the mitochondria produce enzymes that help to break this down into less reactive molecules, but they can still be damaging to the cell if they exceed the level to which they can be neutralised, resulting in a state of oxidative stress. This discovery of cumulative damage to cellular components caused by excess ROS brought free radicals to the attention of the scientific and health communities as a potential explanation for the DNA mutations that lead to cancer, various degenerative conditions and even for ageing itself (Harman, 1956).

This balance between oxidative stress and the production of antioxidant enzymes may also be behind other fundamental life processes such as the sleep-wake cycles that govern circadian rhythms (Reimund, 1994). Neurons have a high energy demand making the brain responsible for as much as 20% of our total oxygen consumption. At such a high metabolic rate, a large amount of ROS are produced that will start to damage the highly specialised architecture of the neuron if it cannot be cleared (Melhuish Beaupre et al., 2022) leading to various neurodegenerative disorders and a known correlation between sleep and dementia (Wong, & Lovier, 2023). To prevent this, melatonin is produced, a powerful antioxidant and inducer of sleep, which can remove ROS while the brain enters a state of lowered consciousness and energy expenditure.

Despite their reputation, it would be a mistake to classify all ROS as bad because they also fulfil some very important roles. One of these is in the immune system where, in response to an invading pathogen, macrophages generate a "respiratory burst," deliberately generating ROS in order to damage the membranes, DNA and cellular components of pathogenic invaders (Luo et al., 2016) while also acting as a signal to resolve inflammation by switching macrophages between their pro- and antiinflammatory forms (Tan et al., 2016). ROS also signals to stem cells what the metabolic requirements of their neighbours are, aiding with their differentiation (Zhou et al., 2014). Another essential function of ROS is the initiation of programmed cell death. When oxidative stress reaches a critical level, the mitochondria initiate a cascade of processes that result in the tightly regulated and controlled breakdown of the cell into fragments that can be consumed by phagocytes (Redza-Dutordoir & Averill-Bates, 2016). This prevents damaged cells from persisting and stops the contents of the cell from spilling out and harming surrounding cells or activating unnecessary inflammation. This means that ROS have a dual role in cancer, where moderate increases can lead to the DNA mutations that cause cells to become cancerous, but high levels will initiate cell death, preventing progression. Some researchers have even tried to reframe cancer as primarily a disorder of mitochondrial dysfunction instead of genetic mutation since this seems to be the initial causative factor and an important determinant of persistence (Seyfried & Chinopoulos, 2021).

## Thermogenesis

Another product of mitochondria is the generation of heat in warm blooded animals. Despite the name, the heat generated by warm blooded animals is not emitted from the blood, nor is it carried by the blood from any central fire, as pictured in many ancient physiological descriptions (Aird, 2011; Hammer, 1999). It is instead generated primarily in mitochondria-rich brown adipose tissue through a process where protons become disconnected (uncoupled) from the process of generating ATP and re-enter the inner mitochondrial membrane, with the energy released as heat (Nicholls, 2021). This process can be tightly controlled through the expression of uncoupling proteins on the mitochondrial membranes which enable the maintenance of a specific core temperature required for homeostasis. This not only makes mitochondria central to the maintenance of our normal temperature, but also behind abnormal states such as fever where inflammatory cytokines stimulate an increase in metabolism by as much as 10-12% for every 1°C (Evans et al., 2015). With mitochondria also being key controllers of inflammation, this creates a two-way relationship between metabolism and immunity.

## Adaptation to Stress (Hormesis)

As the primary sources of energy in our cells, mitochondria play an important role in the adaptation to cellular stresses. Fluctuating energy demands, insufficient nutrients, changes in oxygen levels and interference by drugs all require the mitochondria to respond appropriately. This has been termed mitohormesis, after the process of hormesis by which a low dose of a substance or condition has a beneficial stimulatory effect, while a high dose has an inhibitory or toxic effect (Mattson, 2008). This is because of the origin of mitochondria, which are speculated to have once been free living bacteria that entered into a symbiotic relationship within a larger cell (Callier, 2022). This means that they still behave in similar ways to bacteria: living in

colonies adapting to their environment and evading attempts to kill them. As a result, many activities that apply mild stresses result in adaptation and overall health benefits to the organism as a whole, such as:

• **Exercise**, which causes an increase in energy expenditure, and therefore respiration and ROS, yet results in lower oxidative stress and improved health outcomes (Merry & Ristow, 2016). However, extreme exercise may overtax our mitochondria to their detriment (Flockhart et al., 2021).

• **Fasting**, which involves periods of nutrient deprivation that would be harmful if taken to an extreme but appears to improve our mitochondrial function and even reverse metabolic disorders at the right dose (Kolb et al. 2021).

• **Adaptogenic herbs**, which may interfere with mitochondrial function directly or imitate stress signalling molecules resulting in resistance to an actual stressor when it occurs (Tian et al., 2022).

• **Drug resistance**, where the cells adapt to compensate for the drug's effects. This is especially significant in chemotherapy where drugs aim to target the dysregulated metabolism of cancer cells and trigger cell death, but the mitochondria of the surviving tumour may adapt, shifting towards a more normal respiration making it more difficult to target (Jin et al., 2022). In addition, mitochondria provide the main fuel for drug efflux transporters making mitochondrial dependent cells more resistant to a wide array of drugs (Bokil & Sancho, 2019).

## Hormesis in Chinese Medicine

Hormesis appears to be an important mechanism of many traditional Chinese medical techniques. *Su Wen 2* states that:

> ***"the sages did not treat those already ill, but treated those not yet ill, they did not put in order what was already in disorder, but put in order what was not yet in disorder (trans. Unschuld & Tessenow, 2011), "***

suggesting that building resilience was preferable to curing disease. The ancient focus on practices to extend life (*yang sheng* 养生) which are recorded among the Mawangdui manuscripts (168 B.C.E.) and continue to be popular today (Dear, 2012) also suggests that, even if the terminology was unfamiliar to them, the focus of this resilience was mitochondrial since they are the primary drivers of ageing and senescence. The interventions used also suggest this, being mostly methods of inducing hormesis. Examples found in the literature include exercises, meditation, fasting, manual therapies and herbal remedies.

### Exercise

Exercise is one of the methods that has been researched most extensively with regard to mitohormesis. The increased energy demand which outstrips the mitochondrial supply raises oxidative stress that triggers an adaptive response. The mitochondria reproduce and reorganise into a larger, tighter network which can provide greater energy production and increased antioxidant enzymes (Merry & Ristow, 2016). These adaptive changes are especially prevalent in mitochondria rich high energy tissues such as the heart (Wu et al., 2019), skeletal muscle (Gan et al., 2018) and the nervous system (Sujkowski et al. 2022), improving the markers of ageing (Garatachea et al., 2015) and subsequent risk of many age-related diseases (Jia et al., 2023). Many forms of exercise have been researched in relation to promoting this response, including Taiji (Rosado-Pérez et al. 2021). However, dose is essential and some evidence has emerged that excessive endurance training may be detrimental to mitochondrial health (Flockhart et al., 2021).

Meditation is another form of exercise that appears to follow a hormetic pattern. Studies on meditation students have revealed a short term decrease in oxygenation followed by a sustained increase (Bernardi et al., 2017) and many Chinese meditation techniques for extending life focus on breath control practices (Needham & Lu, 1983) which will likely achieve this same result. Furthermore, training the body with intermittent hypoxia may improve the outcomes from ischemic conditions through preconditioning (Boengler et al., 2018) implying a mitohormesis response. Some other practices which involve hyperoxygenation may also trigger hormetic responses through different pathways but with similar results since mitochondria favour a very precise balance of oxygen and both hypoxia and hyperoxia can lead to increased oxidative stress (Burtscher et al., 2022). Taiji, qigong and other yangs heng systems of meditative exercise are likely to involve mechanisms from both physical exercise and meditation simultaneously.

## Fasting

Fasting has a similar effect to exercise except that instead of increasing energy demand, the hormesis response is initiated by restricting glucose. This has been observed in cellular and simple organism models where limiting glucose supply causes the mitochondria to adapt, switching to a greater dependence on fat metabolism while also reorganising into more efficient networks and resulting in reduced markers of senescence and increased lifespan (Yun & Finkel, 2014). Fasting and low carbohydrate ketogenic diets have become popular areas of research and practice for their potential to improve many aspects of metabolic health and the outcomes of metabolic diseases with mitohormesis being proposed as the main mechanism (Zhu et al., 2022; Miller et al., 2018).

While modern Chinese medicine has not emphasised fasting as much as other traditional medical systems, the potential benefits have drawn attention to several historical references of "avoiding grains" (*bigu* 辟穀) to extend life. The earliest source comes from *Zhuangzi* (c. 3rd century BCE) who refers to a holy man that "doesn't eat the five grains but sucks the wind, drinks the dew (*Zhuangzi*: 1, trans. Watson, 2013)" and attains extraordinary powers from this practice. The first manual to describe the practice is *Eliminating Grain and Eating Qi* (*Que Gu Shi Qi* 卻穀食氣, from the Mawangdui tomb manuscripts sealed 168 B.C.E.) which describes replacing grains with *shi wei* 石韋 (*Pyrrosia lingua leaf*), gradually reducing this herb, to replace all food with breath alone (Harper, 1998).

There appears to be some acknowledgement of a hormesis principle at work in the ancient writings on *bigu*. *Ling Shu* 56 states: "When no grain enters, after half a day the qi will weaken. After a full day they are present only minimally (trans. Unschuld, 2016)," and Ge Hong (c. 320 C.E.) acknowledges this saying that initially people become weaker and only after a time do they feel the benefits, but that it only works if one does not replace the grains by feasting on meat, fruits and wine (Ware, 1966). This seems to imply an understanding that a minimal food intake is potentially harmful and stressful on the body but which can, under the right conditions and dosage, lead to greater resilience and health.

These ancient texts also seem to foretell the double edged nature of carbohydrates. While they are necessary for providing the *gu qi* required for the body to function, they also lead us to early death. In the words of *Eliminating Grain and Eating Qi*: "Those who eat grain eat what is square; those who eat vapor eat what is round. Round is heaven; square is earth (trans. Harper, 1998), implying that the consumption of grain leads our bodies back to the earth. The *Huainanzi* (139 B.C.E.) states that: "Those that feed on flesh are brave and daring but are cruel. Those that feed on qi [attain] spirit illumination and are long-lived. Those that feed on grain are knowledgeable and clever but short-lived. Those that do not feed on anything do not die and are spirits (trans. Major et al., 2010)." Although no reason is ever given by classical authors for why grains are singled out as shortening the lifespan, it would appear that their observations were leading to the same conclusions as many researchers today are coming to: by oversupplying our mitochondria with the carbohydrates they use for fuel, they are not encouraged to function at their most efficient which can lead to mitochondrial dysfunction and the development of many non-communicable causes of ill health. (Clemente-Suárez et al., 2022)

Exactly what constitutes *bigu* today is the matter of some debate. Some take the term literally to refer to avoiding only grains but with no restriction on fruit, vegetables, nuts and seeds, adopted by some as a long term low carbohydrate ketogenic lifestyle (Wang, 2017). Others use the term to refer to brief periods of consuming water only (Fang et al., 2021), or supplemented with fruits to but still constituting extreme low calorie fasting (Hong et al., 2021; Tang et al., 2021) with a return to a normal diet after a few days. Most report favourable outcomes in terms of cardiovascular and metabolic markers of health.

## Manual Therapies

Research into the hormetic effects of manual techniques such as massage and acupuncture are scarce but several factors suggest they may involve mitochondria. The redness that appears around a needle or after some massage techniques imply a mild inflammatory reaction and the stimulation of *deqi* sensations suggests the stimulation of nerves, yet the end result is often a reduction in pain, inflammation, oxidative stress and protection from neurodegeneration and excitotoxicity (Zhao et al., 2021; Fu et al., 2024). Mitochondrial constituents and byproducts of respiration have been identified as signalling molecules that signal damage to the cell when released into the external environment and promote inflammation (Marchi et al., 2023). The precise levels of these have been suggested to initiate different phases of inflammation and healing, with their obstruction resulting in constantly raised levels that may prevent complete recovery and result in chronic disease (Naiveuax, 2023). Neurons are also highly energetic cells which require unique mitochondrial solutions to

handle their unusual architecture (Misgeld & Schartz, 2017) so their stimulation is likely to induce a mitohormesis response protecting them from future harm and excitotoxicity. The possibility that hormesis may be the mechanism behind manual therapies is not new (Zilberter et al., 2013) but little research seems to have been conducted to elucidate this.

Another manual therapy that is likely to elicit a mitohormesis response is cupping and *gua sha*. The petechiae formed as a result from the extravasation of blood into the extravascular tissue (Lowe, 2017), is similar to the formation of a bruise. The iron in the extravasated haemoglobin reacts quickly with ROS to produce even more potent hydroxyl radicals and induces a temporarily heightened state of oxidative stress that serves to make any open wound a more hostile place for invading microorganisms (Jeney et al. 2013). Following the theory of hormesis, the mitochondria in these tissues will compensate for their environment of heightened oxidative stress by increasing the production of endogenous antioxidant enzymes (Ristow & Zarse, 2010). This will be accompanied by the breakdown of haemoglobin into biliverdin and bilirubin, both antioxidant substances, resulting in a net antioxidant effect as the marks turn brown and yellow.

A brief mention of moxibustion is also relevant here although too complex to explore fully. Recently a lot of interest has been generated in the ability of low level visible red and near infrared spectrum of light to modulate mitochondrial function, termed photobiomodulation. The mechanisms are not completely clear but it appears to interact with chromophores within the mitochondria to increase ATP, ROS and nitric oxide production leading to enhanced cellular repair and survival, particularly in hypoxic or stressed cells (Barolet et al., 2023).

The majority of the heat felt by indirect moxa and infrared lamps is from radiated infrared light, some of which is in this near infrared region which may be enough to stimulate this response. However, the majority is within the mid- and far range (Chen et al., 2023) which introduces more heat. Indirect moxa can cause temperatures to reach up to 65℃ on the outer skin and 45℃ in the subcutaneous layer with direct methods sometimes much higher (Deng & Shen, 2013). Cells function within a narrow temperature range, outside of which proteins misfold including those in the electron transport chain, antioxidant defences and those involved in cellular repair (Slimen, 2014).

To prevent this, heat shock proteins are transcribed that act as chaperones to prevent misfolding and refold the denatured proteins (Kurop et al., 2021). Many diseases are influenced by misfolded proteins suggesting that stimulating this response could have potential therapeutic applications (Hu et al., 2022). From the limited studies done, moxibustion does appear to increase the expression of heat shock proteins, modulating the cell cycle and preventing cell death (Choe et al., 2018). This also implies a hormetic response that involves mitochondria although much more research needs to be done on specific mechanisms and outcomes to be certain..

## Herbal Medicine

Many herbs contain antioxidant substances which can affect oxidative stress in complex ways. Since ROS are important signalling molecules, initiating cell differentiation, adaptation to exercise and the apoptosis of defective cells, it may be no surprise that lowering oxidative stress as a blanket strategy may have unwanted side effects (Li, Fasipe & Laher, 2022; Salehi et al., 2018). Furthermore, some phytochemicals normally expressed as antioxidants can have dual effects and even be pro-oxidant under the right conditions (Sotler et al., 2019). This will be explored fully in the next installment of this series and so only a brief introduction is given here.

Hormesis may be an important paradigm in other areas of herbal medicine too. Besides the role of adaptogens mentioned above and explored more thoroughly in part 3 of this series, some herbs are known to produce different effects at different dosages, suggesting a hormetic effect (Wang et al., 2018). The sovereign-minister-envoy scheme of composing formulas may have been influenced by this observation, whereby the sovereign herbs given at the highest doses may have an inhibitory effect, while the envoys and messengers may be inducing a stimulatory response.

## Cryotherapy

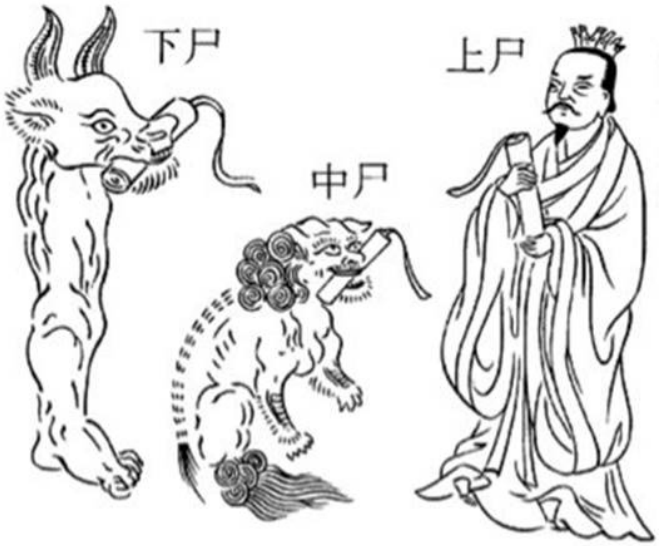
The use of cold to stimulate mitohormesis is worth mentioning for its near complete absence in the Chinese medicine literature and the aversion of TCM practitioners to its use. Considering how many other

modalities of Chinese medicine are using mitohormesis as a mechanism, it is surprising that this one is missing. The only mention in ancient sources is a reference from Ge Hong that those who practiced *bigu* fasting "could withstand wind, cold, heat, or dampness, but there was not a fat one among them (trans. Ware, 1966)," suggesting they exposed themselves to the elements without ill effect and maintained a low weight. Given that many of these people retreated from civilization to the mountains, which were considered sacred places where immortality could be found, a tolerance for cold seems an implicit part of the practice. A living tradition that correlates to this is the practice of *g-tummo* meditation among Tibetan monks who train to resist the cold and even dry wet sheets placed over their bodies while in subzero temperatures to demonstrate their abilities (Kozhevnikov et al., 2012).

Theories of the mechanism of cryotherapy are similar to other forms of hormesis. The need for an adaptive response to generate more body heat triggers growth of mitochondria in adipose tissue and increased expression of uncoupling proteins that cause their energy to be translated into body heat instead of ATP (Chung et al., 2017). Some Chinese medical proponents of cold water immersion therapy have developed similar theories using Chinese terminology: that exposure to extreme y*in* causes a reactive stimulation of *yang* and *wei qi* (Berry, 2023), while others warn of potential long term harm to *yang* (Chiu, 2024). Both may be correct based on the description of the breath as being like a bellows that can make the inner fire burn quickly or slowly, where the "quick fire shifts and slow fire calms (Lu, 1999)," suggesting that the breathing used by Tibetan monks and "iceman" Wim Hof (Citherlet et al., 2021) is utilising Kidney *yang* to generate heat and expel cold, but without a substantial existing supply of *yang*, or supplemental practices to foster it, it will result in depletion or cold damage. Therefore, it seems that dose, duration, the pre-existing health of the practitioner and supplemental practices are important considerations as to whether it has a beneficial or harmful effect.

## The Three Corpse-Worms and Metabolic Reprogramming

Several of these practices come together in the concept of eliminating the three corpse-worms (*san shi* 三尸 or *san chong* 三蟲 ). This ancient concept was understood to involve parasites that inhabit the three *dan tian* from birth, being the death delivering counterpart found at the centre of these sources of life (Huang, 2011). They would encourage overindulgence in worldly pleasures to the detriment of our health, revelling in the putrefaction of our bodies caused by decadence. Early concepts focused on controlling them through ritual, staying awake at nights when they would report our misdeeds to heaven, inciting punishments of ill health and shortened life upon us, but would later become considered in more medical terms.)




**Visual interpretation of the Three Corpses from the Scripture on Eliminating the Three Corpses and Nine Worms to Preserve Life *(Chu San Shi Jiu Chong Bao Sheng Jing* 除三尸 九蟲保生經*, c. 9th century)***

Early medical writings on the three corpse-worms attempted to poison them with highly toxic herbs. Ge Hong advised several formulas containing cinnabar (*zhu sha* 朱砂; mercury sulfide), stating that "If you wish to banish [the three corpses] from your body, you should take cinnabar" (Ware, 1966) while Sun Si-Miao (d. 682 C.E.) favoured poison oak lacquer (*sheng qi* 生漆; *Toxicodendron vernicifluum*) along with rhubarb root (*da huang* 大黄; *Rheum palmatum*) in his recipes to expel them (Maspero, 1981). Other traditions, such as the late 3rd century *Great Numinous Treasure's Array of the Five Talismans* (*Tai Shang Ling Bao Wu Fu Xu*, 太上靈寶五符序) emphasized Indian pokeweed root (*shang lu* 商陆; *Phytolacca acinosa*) as the only medicine powerful enough to expel them, taken in doses that may have been hallucinogenic and caused violent bloody diarrhoea acting as evidence of their expulsion (Raz, 2012). However, this text also introduces a shift back to ritual techniques, stating that the superior method is to "ingest the five sprouts," which it describes as invoking the pure essences of the five directions with chants, inhaling them, imbuing them into the saliva and then swallowing it to absorb them into the body. This is

similar to the practices *Zhuangzi* describes as accompanying *bigu*. Although there are hints that the two practices of *bigu* and expelling the three corpse-worms were connected in early writings, they became explicitly intertwined in the 9th century Classic of the Yellow Center (*Zhong Huang Jing* 中皇經 , 9th century) where almost identical wording that described the expulsion of the three worms through the ingestion of *shang lu* is applied to *bigu*, including the subsequent ingestion of the "five sprouts" (Eskildsen, 1998). *Bigu* subsequently became the main method of starving the three corpse-worms, understood to feed on the grains as they fermented in our intestines, before expulsion with internal and external alchemy practices.

One piece of evidence that suggests the practices of longevity, fasting and the expulsion of the three corpse-worms were linked in earlier times, and that non-toxic herbs could be used to support all three comes from the Divine Farmer's Materia Medica Classic (*Shen Nong Ben Cao Jing* 神農本草經, c. 100-200 C.E.). Many herbs included within its superior and middle classes provide actions attributed to prolonged use, which include the ability to stop hunger (*bu ji* 不饑), lighten the body (*qing shen* 輕身), stop or resist ageing (*bu lao* 不老 or *nai lao* 耐老), stop forgetfulness (*bu wang* 不忘) and extend the years (*yan nian* 延年). Furthermore, several herbs in all categories specifically mention that they "expel (*qu* 去)" or "kill (*sha* 殺) the three worms (*san chong* 三蟲)" and "hidden corpses (*fu shi* 伏尸)" suggesting that longevity, fasting and expelling the three corpse-worms were related concepts practiced among the author's community. Taken together they imply that supplementation with herbs was connected with a protracted fasting regime to attain longevity, maybe by providing the necessary slow release nutrients to assist people adjusting or persisting with this regime (Lu et al., 2020). Complementing regular fasting with the ingestion of many plant based polyphenols and regular spiritual practices that may have involved breath induced hypoxic states or ritual exercises, are all reminiscent of techniques recommended today for maximising mitochondrial health through mitohormesis (Casanova et al., 2023).

Among the herbs said to stop hunger, several are worthy of note. Wild goose fat (*yan fang* 雁肪; *Anser cygnoides*) is mentioned supporting the notion that carbohydrates are being substituted with fats to promote ketogenesis, especially considering the absence of grains being suggested for prolonged use. In fact, rice is not mentioned in the text at all and among the grains that are listed, only sesame (*hu ma* 胡麻*; Sesamum indicum*) and hemp (*ma fen* 麻蕡; *Cannabis sativa*) are given superior status and advised for prolonged use, but not in relation to stopping hunger.

Herbs such as *bai zhu / cang zhu* (*Atractylodes spp*., the text does not differentiate) and *fu ling (Poria cocos)* are also said to stop hunger, which seems counterintuitive since they normally stimulate appetite. However, these herbs have a high polysaccharide content which can modulate the gut microbiota (Qian et al., 2024; Ng et al., 2024), potentially preventing the starved gut microbes from releasing metabolites that trigger sensations of hunger in their host (Han et al., 2021). No studies have specifically looked at the effects of these herbs on the microbiome in fasting but this effect could have been observed by fasting practitioners who realised that these helped their hunger without interfering with the results of their fast. Lastly, the inclusion of Chinese yam (*shan yao* 山药, *Dioscorea polystachya*) and amaranth (*xian shi* 莧實; *Amaranthus tricolor* seed) stand out for both containing ~60-65% starchy carbohydrates (Epping & Laibach, 2020; Zhu, 2017) while also being listed as stopping hunger if taken for a prolonged time. This seems to contradict the idea that the authors practiced a low carbohydrate diet since it could consist of large quantities of these starchy foods instead, but these entries, like most in the *Shen Nong Ben Cao Jing*, contain foraging advice rather than cultivation tips. If foraged and not grown, they would be eaten in much smaller quantities, possibly dried and carried as a permissible high quality carbohydrate source for prolonged use. These exceptions, the exclusion of rice and most other grains which would surely have been easier methods to end hunger if available, and the inclusion of foraging advice, suggest that the 'prolonged use' indications were describing a forager's *bigu* diet that aimed at being maintained, and not short periods of extreme abstinence.

*Ling zhi (Ganoderma lucidum)* seems to hold a special place in the *Shen Nong Ben Cao Jing*, being divided in five types according to colour with all of them possessing the ability to lighten the body, stop ageing, extend the years and even become immortal. The red variety most commonly used today also has the attribute of stopping forgetfulness. These suggest it was recognised to have powerful anti-ageing effects. Modern literature supports this with numerous anti-ageing effects identified in medicinal mushrooms in general (Luo et al., 2024; Shevchuk et al., 2023) and *Ganoderma lucidum* in particular (Wang et al., 2017), including immunomodulatory, cancer protective and neuroprotective actions, which suggest mitohormesis as a key mechanism.

.There are many others mentioned with a variety of actions attributed to them with prolonged use that suggest specific mitochondrial effects. Many state that they "lighten the body" (*qing shen* 輕身) which has often been taken to refer the development of supernatural powers like flight or superhuman endurance (Yang, 1998). This could also be read literally as enhancing the fasting effect to burn fat, as Ge Hong states that among *bigu* practitioners: "there was not a fat one among them (trans Ware, 1966)." A thorough study of these herbs and their effects in relation to either stimulating or enhancing fasting-induced hormesis, or aiding the practitioner to endure the fast by modulating the microbiome, will surely reveal some useful information on both the meanings of these passages and potential uses in metabolic disorders today.

Despite the supernatural descriptions of traditional narratives, the principle of the three corpse-worms and their treatment still seems relevant today. Many of the leading causes of death, including cardiovascular and neurodegenerative disorders, complications of diabetes, cancers and susceptibility to Covid-19 (WHO, 2024) are the result of mitochondrial dysfunction which itself stems from poor diets and sedentary lifestyles. Diets high in sugar and refined carbohydrates combined with low levels of physical activity fail to induce mitohormesis leading to poor mitochondrial function. Although maintenance of an optimal mitochondrial function to prevent disease is best, once developed, fasting or ketogenic diets may be a valid treatment option in many cases (Sethi et al. 2024; Zhou et al., 2022; Jensen et al., 2020; Hong et al., 2021). Meditation as an accompanying practice also seems a reasonable addition, acting as a second form of mitohormesis through fluctuations in oxygen while also helping to foster the discipline required to endure the fast and prevent future overindulgence (Katterman et al., 2014). Furthermore, if "ingesting the five sprouts" is interpreted symbolically as incorporating life-affirming practices associated with each of the five phases into your life to nourish their corresponding *zang* within the internal landscape of the body, then it appears that the process of expelling the three corpse-worms is nothing less than a complete metabolic reprogramming through lifestyle changes and herbs with mitohormesis as its primary mechanism.

## Mitochondria and Qi

If we consider how pivotal mitochondria appear to be or health, longevity, disease and healing, it comes as no surprise that parallels have been drawn between mitochondria and fundamental Chinese medical concepts such as qi. This was first suggested by the pioneering mitochondrial geneticist Douglas C. Wallace (2008) and has been followed by several studies supporting this idea (e.g. Wong et al., 2012; Leong et al., 2018; Chen et al., 2020). If we consider the standard TCM model for the generation of qi then there certainly seems to be some similarities: *Gu qi* extracted from food is combined with *da qi* or *kong qi* from the air to form *zong qi* that becomes the basis for all other forms of qi. This seems to parallel the transformation of glucose and fatty acids obtained from food and oxygen from our breath into ATP in the mitochondria (Boggie, 2007; Wagner & Cox, 2009). The more recent discoveries that mitochondria also regulate many aspects of our immune system as well as providing energy necessary for most biological functions also seems equate to the notion that, once *zong qi* is transformed into *zhen qi*, its clear and turbid factions become *ying* and *wei qi*, the nutritive qi that flows through the channels providing the essential energy for maintaining life and the defensive qi that circulates outside, guarding the exterior. Other authors have suggested that the role of mitochondria in thermogenesis, growth, ageing, circadian rhythms and immunity make them more comparable to *yang qi* specifically (Luo et al., 2022).

Both of these comparisons do not capture the fundamental essence of qi. *Qi* is not an exclusively biological phenomenon but a multi-valent term that draws together many different ways of understanding the world, including cosmological, political, philosophical, natural scientific and phenomenological models, as well as the medical-physiological (Stanley-Baker, 2022). Many of these have no relation to mitochondria and if mitochondrial function becomes equated with *qi* then we run the risk of narrowing the definition of *qi* to that which fits the mitochondrial model, at the expense of others which arguably have even greater value. This lesson should have been learned from the early translators of Chinese medicine who used their own vitalist doctrines to translate *qi* as "vital energy" which then caused many in modern health fields to deregard *qi* once vitalism was disproven (Kendall, 2008). *Qi* should be understood on its own terms, but it does provide a launching point from which to generate hypotheses about how herbs might affect mitochondrial function, observing how certain classes of herbs that influence *qi* in a particular way might be predisposed to affecting mitochondria in a particular way.

To achieve this, I will spend the next two articles in this series looking at two of the main classes of herbs that affect mitochondrial activity: antioxidants and adaptogens, and how they connect with Chinese medical concepts and classes of herbs. In the final article, I will look at how mitochondrial function can be used in evaluating the quality of herbs and formulas by measuring their effects on biological systems instead of using marker compounds. This instalment has set up a foundation for understanding the way mitochondria respond to interventions, paving the way for future examination of particular herbs and classes. In the next part, I look forward to taking you on a deep journey into the role of antioxidants in Chinese herbal medicine.

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