

The voluntary mechanism

The involuntary estrogen-balancing mechanism that we have just looked at has a voluntary side to it to the extent that a woman can have some control over the amount and the type of estrogen that her body is making through her amount of body fat (the more fat, the more estrogen) and how often she falls pregnant (and therefore the number of ovulations that she has, and therefore the amount and type of estrogen being produced). And as we will see in the next section of this book, these factors, particularly the ovulation factor, are not insignificant contributors to the problems of the modern woman.

But there is another voluntary aspect to this story which goes right to the heart of the current problem. The involuntary balancing mechanism has a powerful capacity to match estrogen needs to demand, but it was never intended to work on its own. It was meant to work in tandem with another mechanism. That other mechanism, while not quite as potent and dramatic in its actions as the involuntary mechanism, is nevertheless an essential contributor to the overall balancing mechanism. We are referring to this mechanism as the *voluntary estrogen-balancing mechanism* because it is entirely under our control as to the strength of its action.

The voluntary mechanism has two main functions. The first function applies particularly to the pre-menopausal woman, and this is to back-up the involuntary mechanism if and when it comes under pressure of an excess of estrogen. The competitive-inhibition aspect of the involuntary mechanism that we looked at does the heavy-lifting in this respect, but there are plenty of times when even it comes under pressure. In that situation, the voluntary mechanism provides a back-up layer of protection that serves to protect the body from over-stimulation by estrogen.

Its second role applies to the post-menopausal woman. This is the reverse situation...a woman now needs all the estrogenic help she can get, and that is exactly what the voluntary mechanism does. It provides a supplementary source of estrogen that is insufficient to stop the menopause, but goes a long way to meeting the estrogenic needs of the non-sexual tissues.

You won't find a description of this involuntary mechanism in medical textbooks, largely because it has been scientific anathema that it is possible to exert voluntary control over our hormones. Nevertheless, evidence for its existence has been staring us in the face for some decades. That evidence is contained in many thousand publications in scientific journals that report on different aspects of this voluntary mechanism, but in a classic case of not seeing the wood for the trees, somehow this wide body of evidence has failed to be seen by scientists and doctors in the context that is being presented here.

Another reason hindering its recognition by the scientific and medical communities is that some of the evidence for the voluntary mechanism has been adopted by less conventional health-care providers who haven't done their cause any good by over-playing the importance of the evidence and presenting it as the preferred alternative to modern medicine. But like most things in life, the truth lies somewhere in the middle, and that is the basis of the concept being presented here. Both mechanisms are important, and both need to be in balance for the estrogen system to function properly.

This auxiliary estrogen-balancing system is based on chemicals we will call hereafter, *non-steroidal estrogens* (or NSEs for short). By this we mean that they are not based on the steroid chemical structure that marks estrogens like estradiol. Non-steroidal estrogens don't come from cholesterol like estradiol does. Non-steroidal estrogens and steroidal estrogens are remarkably similar in structure, so much so that they are able to bind to the estrogen receptor in the same way as steroidal estrogens.

As you read this, your body almost certainly contains fairly high levels of these chemicals. By 'fairly high', we are talking of the order of several thousand times higher than your steroidal estrogen levels. The level of steroidal estrogens such as estradiol in your blood is roughly equivalent to the amount of chemical you could put on the top of a pin, dissolved in an Olympic swimming pool. The level of non-steroidal estrogens is like throwing 3 cupfuls of chemical in the pool.

These non-steroidal estrogens are distant relatives of estrogens such as estradiol and share most functions in common with steroidal estrogens. They represent the body's second estrogen system.

Most people would recognise non-steroidal estrogens by their more common generic chemical title, *flavonoids*, or the highly beneficial anti-oxidants that we obtain from brightly-coloured fruits and vegetables. But flavonoids are far more important to humans than simply as anti-oxidants, and it is that importance that is behind their role as the pre-eminent 'balancers' of estrogen function in humans.

Not all flavonoids are estrogenic. In fact, the vast majority of the 5,000 or so known flavonoids aren't. But enough are, and fortunately the human diet can deliver the relevant ones in reasonable quantities, and it is these that we rely on to provide the voluntary estrogen-balancing mechanism.

NSEs constitute a primitive estrogen system in our bodies. As we will learn in more detail later, they are the original sex hormone system that Nature created to govern reproductive behaviour in all primitive animal life. The estrogen, progesterone and testosterone hormones that our bodies now make are nothing more than sophisticated versions of flavonoids, providing little more than a fine-tuning function. That primitive estrogen system – the flavonoids – remains in our bodies to the present day, providing the same basic sex hormone-regulating function that sustained animal life in our primitive beginnings. So rather than being a minor player or even optional system in our bodies, flavonoids are major league players in estrogen balance in our bodies.

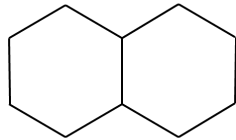
NSEs interact with steroidal estrogen (SE) function in four important ways as follows.

NSEs and SE (steroidal estrogen) interaction

1. NSEs are weak estrogens.

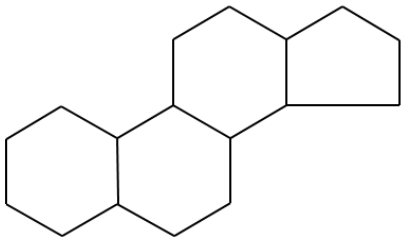
NSEs are weak to very weak estrogens. The strongest ones are about as strong as estriol (that is, 100x weaker than estradiol), while others range down to about 10,000x weaker than estradiol. It is not clear just how many NSEs there are, but it appears that only a dozen or so are the main players, and these are estrogenic within the range 100x – 1000x weaker than estradiol.

NSEs are estrogenic because they look like SEs, and they look alike because they are in fact first cousins. Both types of estrogens are built on the same chemical foundation comprising two phenolic rings, one of the most common building blocks in Nature. For those who have forgotten their organic chemistry, a phenolic ring is composed of 6 carbon atoms. Two such rings joined together are known as a diphenolic structure.

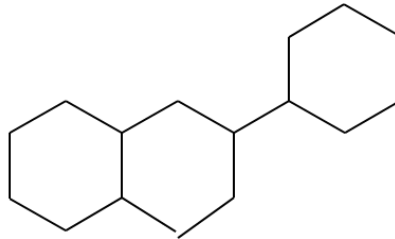


diphenolic structure

NSEs and SEs are both referred to in chemical terms as diphenolics, because they both are constructed on this common platform, as shown below. The difference lies in the way additional phenolic rings are attached to the underlying diphenolic structure. In the case of the structure on the left, the overall structure is referred to as a steroid. In the case of the structure on the right, it is a flavonoid.

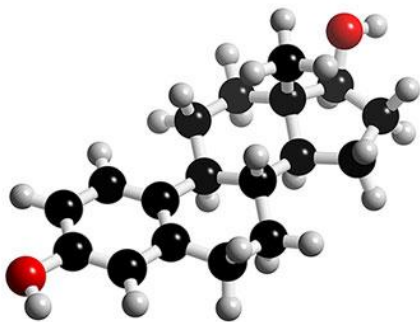


Steroidal estrogen

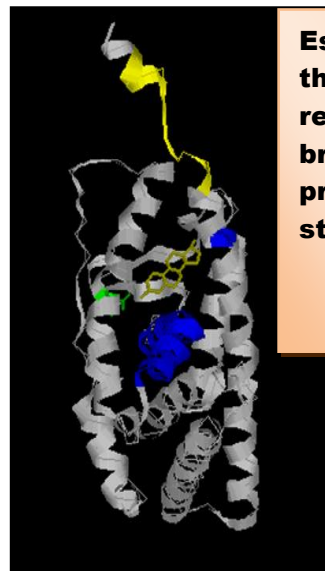


Non-steroidal estrogen

Those flavonoids that are estrogenic are so because their 3-dimensional shape is almost identical to estradiol. The ability of a compound to enter and activate the estrogen receptor is related to its physical shape, hence the key-and-lock analogy. The structures that we see above are 1-dimensional views only and are done just for convenience. That is how chemists generally describe molecules. But for biologists interested in how molecules interact with cells and trigger certain functions, the 3-dimensional structure or shape is all-important.



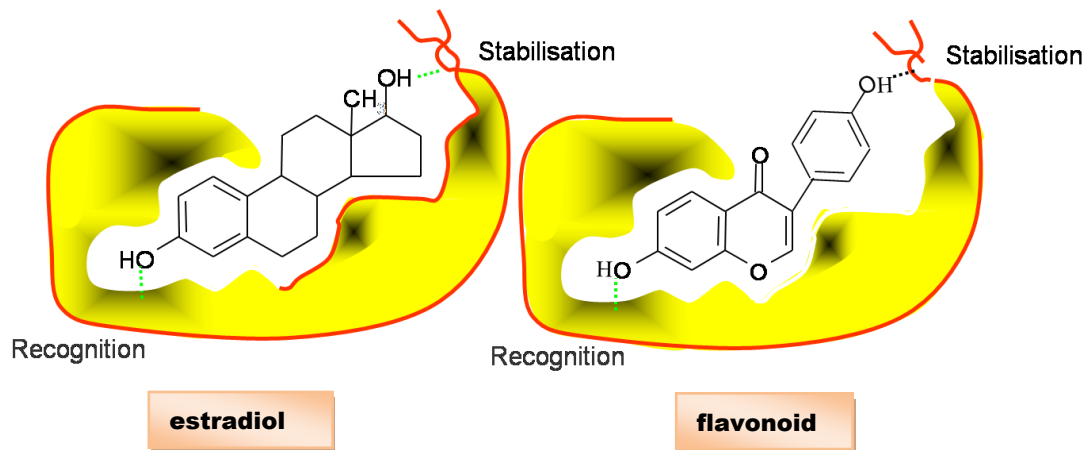
3-D view of estradiol



Estradiol in the estrogen receptor bridging two protein strands

The docking site on the estrogen receptor involves two specific spots on the folded protein chain where the two terminal ends of the hormone attach. The insertion of the hormone into those two spots acts like a rigid rod stabilising the flexible protein chain, and that stabilisation results in the release of the receptor's trigger. The critical thing in this case is the distance between the two docking sites. That is represented by the distance between the two (red) oxygen atoms on the estradiol molecule in the picture above.

NSEs are able to act as estrogens, in part because they have an almost identical 3-D shape to estradiol, but particularly because the distance between the two terminal ends is almost identical. The diagram below is a representation of an estradiol molecule (on the left) and a flavonoid molecule (on the right) attached at both ends to the two docking points of the receptor. Note that one end of the flavonoid molecule has had to bend slightly to slot in, and it is this bending and the tension that it imposes on the receptor site that means that it doesn't allow the receptor's trigger to be released fully. That is exactly the same situation that applies to the weaker SEs such as estrone and estriol. They don't have the identical shape and length as estradiol, and therefore don't fully release the receptor trigger.



The comparatively weak estrogenic strength of NSEs might suggest that they would have little impact in the body. But the reality is the opposite. Estriol, the weakest of all the SEs, is regarded as making a significant contribution to estrogenic activity in the body. Certainly its contribution is overwhelmed by that of estradiol in the pre-menopausal woman, but in the post-menopausal woman, its estrogenic contribution alongside that of estrone is not inconsequential. When you consider that some of the NSEs have equivalent estrogenic potency to that of estriol and are present in blood at levels several thousand times higher than estriol (or estrone for that matter), then the potential estrogenic potency of this pool of NSEs is considerable.

On the opposite side of the coin, NSEs are effective competitive inhibitors of estrogen function. Weak estrogens such as estriol and the 2-hydroxy estrogens are able to exert meaningful inhibition of estradiol at a ratio of about 4:1. That is, we only need about four times as much estriol as estradiol to have some meaningful reduction in the ability of estradiol to bind to the estrogen receptors. When you take into account the very high ratio of NSEs to SEs in blood, the potential of this second type of estrogen to competitively inhibit the SEs is considerable.

This apparent paradox of a compound acting as both an estrogen and an anti-estrogen is something we looked at earlier. And as we discovered, it is all part of an overall balancing mechanism where the body has a pool of different estrogens of differing strengths that are capable of cushioning and complementing each other. NSEs are simply part of that pool, and a not inconsiderable part when you consider their numerical strength compared to the SEs.

2. NSEs distinguish between *alpha* and *beta* receptors.

The substantial quantities of NSEs in our bodies, begs an important question. Even allowing for the fact that they are cushioning the impact of strong estrogens such as estradiol on the body, they nevertheless are estrogens, and therefore shouldn't their huge presence in the body lead to 'estrogen excess' in their own right?

The answer is, no. And this is because NSEs have a vital feature that isn't shared with their modern estrogen counterparts, and that is that NSEs are able to distinguish between *alpha* and *beta* estrogen receptors.

SEs are unable to make this distinction – they simply identify an estrogen receptor and lock in and activate it accordingly. Flavonoids, on the other hand, are able to bind to both receptors, but to only activate the *beta* receptors in a meaningful way.

That is not to say that flavonoids don't stimulate *alpha* receptors at all, it is just that their impact on *alpha* receptors is incredibly slight. In fact, it is so slight, that extremely large amounts of flavonoids would need to be eaten before they would show any stimulation of the reproductive organs. An example of this exists in the animal world with a condition known as 'clover disease'. This condition was first diagnosed in sheep in Australia in the 1950s. It occurred in sheep that were grazing for several months on pastures rich in certain strains of subterranean clovers. These particular strains of sub-clover were found to contain such enormous quantities of estrogenic flavonoids that animals feeding on almost pure pastures of these particular grasses ended up with evidence of severe disruption of their female sex hormone systems. When the sheep were removed from these pastures and put onto pastures containing strains of sub-clover with normal levels of estrogenic flavonoids, the condition disappeared and the sheep returned to normal reproductive behaviour.

'Clover disease' is an aberration, but it serves the purpose of providing living proof that estrogenic flavonoids do bind to the mammalian *alpha* estrogen receptor. Removing the affected sheep from the sub-clover caused the levels of estrogenic flavonoids in sheep blood to drop 100-fold, which is roughly equivalent to the sorts of levels present in human blood. At that level, the estrogenic flavonoids are not capable of activating the *alpha* receptors in any meaningful way, meaning that the reproductive tissues are not being stimulated by these compounds. However, their ability to bind to the *alpha* receptors remains intact, and in so doing, is providing a highly effective protective blanket against the excesses of the action of SEs on tissues of the reproductive system.

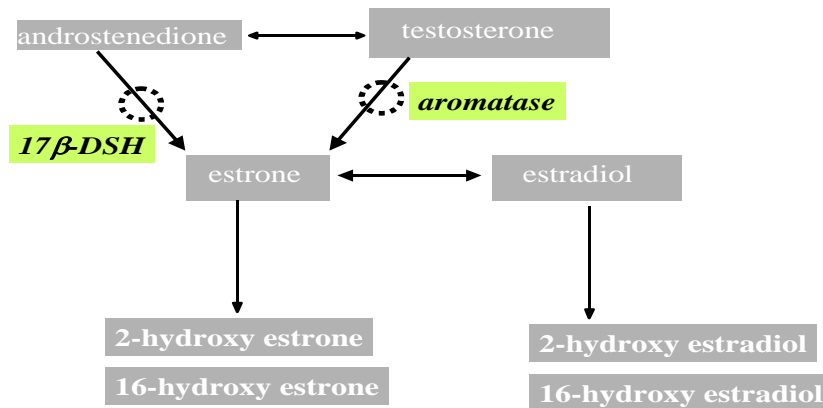
There is nothing odd about this ability of flavonoids to bind to a receptor but not to activate it. It is exactly this principle that has been employed in the development of drugs such as Tamoxifen for the treatment of breast cancer. Tamoxifen was designed to look sufficiently like estrogen that it could bind to the *alpha* receptor, but sufficiently different that once there, it would not activate the receptor. By occupying the receptor but not activating it, the tamoxifen was depriving potent estrogens such as estradiol from working. By separating the breast cancer cells from estrogen, Tamoxifen deprives the breast cancer cells of their main source of stimulation. Flavonoids work on exactly the same principle. In developing flavonoids, Nature simply beat the modern chemists who created Tamoxifen by hundreds of thousands of years.

The story is quite different with the *beta* receptors. Flavonoids bind to these receptors and activate them in exactly the same manner as estrogens. Flavonoids have been shown:

- to induce the relaxation of the muscles in the wall of blood vessels (thereby correcting high blood pressure);
- to induce bone cells to increase their bone-making functions (thereby helping to maintain bone strength)
- to regulate how cholesterol and fats are made and used in the body (thereby reducing the risk of heart disease)
- to maintain the normal structure of the lens in the eye (thereby reducing the risk of cataracts).

3. Flavonoids regulate the production of SEs.

Flavonoids can influence how much steroidal estrogen is made by the body. They do this through inhibiting a number of different enzymes involved in the estrogen production process.



Two such important enzymes are *17β-hydroxysteroid dehydrogenase (17β-DSD)* and *aromatase*. *17β-DSD* is the enzyme responsible for converting androstenedione to estrone and *aromatase* is the enzyme responsible for converting testosterone to estrone. So by dampening down the activities of both of these key enzymes, flavonoids have an impact on the ability of the body to manufacture estrogens. Estrone is the pivotal estrogen that needs to be manufactured to enable all other forms of estrogen to be made. By reducing the level of estrone in the body, flavonoids effectively can lower the amount of raw material required for further production of more powerful estrogens.

It needs to be emphasised that this action of the flavonoids isn't a matter of blocking the production of SEs and depriving the body of the more powerful SEs. The action is more one of dampening down their production in yet another example of how integrated the entire estrogen system is, with the involuntary and voluntary systems working in tandem to deliver a balanced estrogen outcome.

4. Flavonoids regulate the sulfation of SEs.

The fourth and final way in which flavonoids modify how we make and use our steroidal estrogens is via the sulfation pathway. To refresh our memory, sulfation is the process by which SEs are transported around the body and then held in a form of reservoir for later use. Holding them in this form is arguably the most powerful mechanism the body has to cushion it against estrogen surges and falls.

Flavonoids influence this process in two ways. First, they promote the activity of the enzyme, *estrogen sulfotransferase*, which attaches the sulphate group to estrogens in the first place. Then at the other end of the process, flavonoids depress the activity of the enzyme, *steroid sulfatase*, which is responsible for removing the sulphate group from the estrogens in order for them to be activated.

The result of these two activities is to increase the reservoir of SEs being held in the body in an inactive form, and to slow the rate at which they are released from that reservoir to be converted into the more potent forms such as the 16α -hydroxy estrogen forms.

Summary of NSE and SE interaction

Flavonoids contribute to the estrogen hormone system and general health of women in two essential ways –

1. they buffer the impact of estrogen on the reproductive organs, and
2. they provide estrogenic support to the non-reproductive tissues in the absence of estrogen.

These two effects provide the body with the complete *estrogen balancing* mechanism – protecting the reproductive tissues in the younger woman from the ravages of excess estrogen, and providing a support system for the rest of a woman's body following menopause.

The pre-menopausal woman

By dampening down the total amount of steroidal estrogen being made in the body, by promoting the proportion of steroidal estrogen being held in the sulphated reservoir, and by competitively inhibiting the action of SEs on the *alpha* receptors, the flavonoids are exerting a very significant buffering effect on estrogen function in the body.

The potential impact of this effect on the reproductive organs is obvious. The flavonoids are not preventing SEs from working, they simply are acting like a shock-absorber, regulating and lessening the impact of strong estrogens on the breasts, uterus and ovaries as estrogen levels surge and wane.

The post-menopausal woman

But estrogen is good for us... we need it in order to maintain the youthful vigour of all of our tissues ... that without it, our bones get brittle, our arteries get harder and our blood pressure rises unhealthily, our skin gets thinner and drier, our eyes become more crystalline and develop cataracts, and our bladders become weaker. And this is where the flavonoids really shine, because of their ability to activate the *beta* estrogen receptor.

To some extent it isn't going to matter how much steroidal estrogen is present in the body as far as the *beta* receptor is concerned, because the *beta* receptors don't really need estrogen when flavonoids are present. It is not that flavonoids are any better than estrogens for activating *beta* receptors and maintaining the youthful vigour of tissues such as bones and arteries, it is simply that flavonoids are just as good as the SEs in this task.

This action of flavonoids on the *beta* receptor is the means by which the body is able to create menopause. Because without such a back-up mechanism, it makes little sense that Nature would have created menopause. Why make the body generally so dependant upon a hormone that needs to be reduced in mid-life to allow a woman freedom from childrearing, when doing so would only open the rest of the body to a serious hormone deficiency? The flavonoids provided the obvious solution. The fact that these substances come from our diet and don't rely on our bodies to make them, means that as long as we keep eating, then their presence in our bodies throughout life is assured. That meant that Nature could switch off estrogen production in midlife to allow the reproductive organs to become inactive without prejudicing the health of the rest of the body.

That is the ultimate value of flavonoids to the body – to protect our reproductive organs from estrogen without prejudice to the rest of the body.

An evolutionary perspective

To help appreciate the partnership between NSEs and SEs, it is useful to consider the matter from an evolutionary perspective.

Plants represent the vast majority of the history of life on Earth. The emergence of animal life, and mammalian life in particular, represents just a blink of an eye in terms of that history. Across that vast spread of time, flavonoids have served as Nature's primitive but effective sex hormone system. They remain so to this day in plants, serving to control the reproductive behaviour of plants.

Why do plants need sex hormones? Given that plants don't menstruate or get pregnant or lactate or have bones or a cardiovascular system, why would they need weak estrogens? The answer is that plants still need to reproduce, and reproduction no matter how primitive still requires a hormone system to drive it. Flavonoids are the largest single family of chemicals in plants, serving a wide variety of functions in plants, but one of their key roles is to act as plant sex hormones, regulating reproductive activities such as flowering and budding.

But plants also have the ability to manufacture steroidal estrogens - estradiol, estrone and testosterone. These hormones are present in most plants at very low levels, although there are a few notable exceptions. The apple, date and pomegranate contain measurable levels of estradiol and estrone, leading to ancient cultures identifying these fruits as 'fruits of fertility'. Since the apple contains the highest known amount of estradiol of any plant, it perhaps is no accident that it features in legend as the fruit that Eve used to tempt Adam.

Just why plants make tiny amounts of steroidal estrogens is not known, but the interplay between flavonoids and steroidal estrogens is illustrated by experiments where botanists have injected animal estradiol into plants in very tiny amounts and found that they have been able to induce the onset of reproductive behaviour such as budding and flowering.

Further cementing the evolutionary kinship between flavonoids and steroidal estrogens is the fact that the manufacturing process used by plants to manufacture flavonoids and modern estrogens are very similar. In fact, the plant makes flavonoids first, and then uses a couple more chemical steps to convert the flavonoids into estrone and estradiol.

So NSEs and SEs have existed side-by-side in Nature a long time before animal life appeared on this planet. But then along came animal life, and with it the need for the sophisticated and complicated reproductive systems that we see in the higher animal species today. For this level of complexity, a sex hormone system well beyond that of a plant's primitive sex hormone system was required. The development of the mammalian female reproductive system demanded estrogens far more potent than flavonoids that could drive the growth of reproductive organs within a matter of hours when required.

The basis of that increased sophistication was readily available to Nature. Plants already had the mechanisms in place to make more powerful estrogens such as estrone and estradiol, so in the evolution of animal life from plants life, Nature simply preserved and expanded on this manufacturing system to the point of sophistication that we see in today's modern woman. But lest we get too arrogant about our level of sophistication versus that of a plant, just remember that an apple is just as capable of manufacturing estradiol as you are, and in doing so, is using a process not all that differently to you.

As animal life gradually evolved from plant life, there would have been a gradual conversion over time of the biochemical manufacturing process from assembly of flavonoids to that of steroid hormones (estrogens, progesterone, testosterone, cortisone etc.). There would have been little

evolutionary pressure for those early life forms to retain a dual manufacturing capacity because there was such an abundance of flavonoids in the plant kingdom. The same principle applies to virtually all essential nutrients such as vitamins, amino acids and glucose. At one stage, the common ancestor that we animals shared with plants would have had the capacity to make all of these compounds. But early on in the evolutionary pathway our ancestors decided to forgo the need to make such essential nutrients because we could obtain all we needed from plants. Plants do not eat other plants so they therefore need to be totally self-reliant on these life-sustaining nutrients. But once animals evolved the capacity to eat plants, they no longer needed to be as self-reliant as plants. Manufacturing compounds such as vitamins and flavonoids in the body is an energy-intensive process, so where we didn't need to do so, we stopped doing so.

With the reliance by pre-humans on plant material for much of their dietary needs, Nature ensured that we had both forms of estrogen in the bodies to allow the development of a sophisticated female sex hormone system.

And so the perfect partnership was born. The development of powerful estrogens with the ability to sustain a sophisticated reproductive system, along with more abundant primitive estrogens that provided an effective buffering action to those more powerful estrogens, as well as acting as an estrogen support system to the rest of the body when the more powerful estrogens were reduced due to times of stress or menopause.

From our earliest pre-human ancestors 200,000 –300,000 years ago, to our earliest ancestors about 80,000 years ago that began to most closely resemble our current forms, a feature of their biology would have been the large quantities of flavonoids in their bodies. Their hunter-gatherer lifestyle involving the collection of berries, wild fruits, cereals, root vegetables etc. would have provided a regular and substantial supply of flavonoids in their diet.

This meant that large quantities of flavonoids were present in the body at the same time that their reproductive systems were undergoing development and refinement. In other words, the development of the estrogen system was taking place in the presence of an external force having a powerful regulating effect on those estrogens. It is inconceivable that some accommodation wasn't reached in the face of this extraordinary symmetry of effects.

In fact, what this situation did was to provide Nature with a marvellous opportunity. This symmetry between two different families of compounds provided Nature with the luxury of making estrogen a multi-purpose hormone across all parts of the body, but with the opportunity of separating the estrogen needs of the reproductive parts from the non-reproductive parts.

The presence of the flavonoids with their estrogen-cushioning effects would have meant that steroidal estrogen levels could be allowed to surge at different times of a woman's life without risking long-term damage to the reproductive organs. But it also meant that estrogen levels could be diminished (eg. during breast-feeding and after menopause) to allow the reproductive organs to become inactive without compromising the estrogen needs of the rest of the body.

The end result of this evolutionary process is the dual estrogen system that our bodies run on today – a dual system comprising an ancient, primitive estrogen system that traces its beginnings back to the emergence of life itself, combined with a more modern estrogen system that probably also has been around since the beginning of life but which has only flourished since the emergence of animals.