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## Lost Seasonality and Overconsumption of Plants: Risking Oxalate Toxicity

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# Lost Seasonality and Overconsumption of Plants: Risking Oxalate Toxicity

## **Abstract**

In many plants, oxalate crystals are present. These relatively large microcrystals have the potential to inflict mechanical injury. On the other hand, ionic, soluble, and nano-crystal forms of oxalate are readily absorbed. Bioaccumulation in humans is well documented. Crystals and ionic oxalate are associated with pain and both functional and chronic disorders.

Today's many health challenges have led people to select foods purported to be healthier, many of which are high in oxalate. Modern dietary approaches have placed great emphasis on the health benefits of vegetables, nuts, and spices. Many of these are high oxalate foods that are now distributed through a global food system in which seasons have been erased, making harm from dietary oxalate more likely now than ever before. Lack of awareness of this potential creates fertile ground for continued increases in human suffering and public health problems.

## **Keywords**

Amaranthaceae, bariatric surgery, bioaccumulation, biological availability, biomineralization, calcium, calcium oxalate, chronic disease, citrates, crystals, deficiency, Dieffenbachia, diet, fatal outcome, food poisoning, food science, foodborne diseases, fruits and vegetables, humans, hyperoxaluria, inflammation, inflammasome, intestinal inflammation, low oxalate diet, legume, microbiota, microbiome, nuts, oxalate, oxalic acid, oxalosis, pain, plant foods, Polygonaceae, raphides, toxicity, kidney failure acute, kidney calculi, renal, renal insufficiency, renal stone, thyroid, toxicology

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## **Lost Seasonality and Overconsumption of Plants: Risking Oxalate Toxicity**

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### **Introduction**

World-wide, our contemporary health crisis involves the popularity of foods that cause both toxicity and nutrient deficiencies. Usually we think of sugar, trans-fats, and artificial ingredients as central culprits. Yet, one of the most potent toxins that people regularly ingest is naturally occurring oxalic acid and its oxalate salts. In the body, food-borne oxalates not only generate direct toxicity, they also deplete nutrients. This commentary argues for increased awareness of oxalates in foods and cautions against promotion of and regular use of foods high in oxalate.

### **Oxalic Acid, Oxalates, and Calcium Oxalate Crystals**

Oxalic acid is a small 2-carbon molecule (formula  $C_2H_2O_4$ ) that readily donates protons thus forming oxalate ions ( $C_2O_4^{2-}$ ) and oxalate salts. Being a chelating agent for metal cations, it forms soluble salts with the metal ions lithium (Li), sodium (Na), and potassium (K), and with ferrous salts. All other oxalates (notably calcium oxalate) are virtually insoluble at neutral or alkaline pH.

Soluble oxalate and oxalate ions are universally toxic to mammals and easily move across membranes<sup>1-3</sup>. Purified forms have caused rapid deaths (typically accidental) since the early 1800s<sup>4,5</sup>. Being hard to detect, even at doses that rapidly kill a person, oxalic acid was the poison of interest in the very first experimental toxicology study published in 1823 in England by Robert Christison and Charles Coindet<sup>6</sup>.

Free-form oxalate ions, soluble oxalate salts, insoluble oxalates, and mineralized calcium oxalate crystals occur naturally in plants, including food plants, in varying concentrations. Oxalate is also produced in the body in small quantities as a metabolic by-product. A group of rare genetic conditions, the primary hyperoxalurias (PH), causes over-production of oxalate internally with deadly consequences<sup>7</sup>.

A diet with a preponderance of foods containing substantial oxalate has long been known to be dangerous, and sometimes deadly<sup>8</sup>. Oxalate in foods, including rhubarb<sup>9-12</sup>, star fruit<sup>13-15</sup>, and sorrel<sup>16</sup> has been cited as the proximal cause of

human deaths many times. Non-lethal oxalate toxicity is less recognized beyond the growing problem of kidney stones<sup>17</sup>.

### **Toxic Mechanical Injury Due to Calcium Oxalate Crystals in Plants**

The insoluble calcium oxalate crystals in plants come in a wide array of sizes and shapes, including bundles of double pointed needles called raphides<sup>18</sup>. These calcium oxalate crystals are relatively stable minerals serving as durable microfossils of some archaeological interest, being found where other plant residues are no longer evident<sup>19</sup>.

Raphides are known to cause skin irritation, and oral and upper respiratory injury<sup>20</sup>. The non-food plant, *Dieffenbachia*, is a long-recognized and dramatic example. Excellent photographic illustration of oral and upper respiratory damage is offered in a recent report of a poisoning case requiring a 9-day hospitalization due to injuries sustained from brief exposure to a drop of *Dieffenbachia* sap<sup>21</sup>. *Dieffenbachia* possesses a system described as a defensive ‘microscopic blowgun’ whereby the tightly bundled raphides are forcefully ejected (assisted by turgor pressure of cell contents) for a distance of two to three cell lengths when the cells are disrupted. The “Needle Effect” of raphides has been demonstrated countless times, whereby traumatic injury results from the release of the raphides combined with the effects of proteases, soluble oxalate, and other chemical toxins carried on their surfaces and in their grooves in a defensive synergism<sup>22</sup>.

In many plants, including many that we eat, calcium oxalate crystals are present, although there is limited research on the specific forms and quantities of these crystals in foods. Hard and sharp-edged, oxalate crystals take many forms, in varying sizes, beyond the raphide<sup>23-26</sup>. They have the potential to inflict mechanical injury to skin<sup>20</sup>, teeth<sup>27</sup>, and the mucosal linings of the alimentary canal<sup>28</sup>. These crystals may play an unrecognized role in the etiology of gut-associated illness. This type of localized oxalate toxicity involves mechanical abrasion and does not depend on absorption into the body.

### **Oxalates are a likely contributor to many modern health problems**

Unlike the larger microcrystals of calcium oxalate, ionic, soluble and nano-crystal forms of oxalate are readily absorbed into the body<sup>29</sup>, however, a number of dynamic factors influence relative bio-availability<sup>30,31</sup>. A 2013 report of a study using radioisotope-labeled oxalate in rats by Susan Marengo, et al., demonstrated that “doses of oxalate typically considered unimportant have the potential to impact patient health” (p. 464)<sup>32</sup>. These studies and others<sup>29,33,34</sup> show that the typical amounts of oxalate in our diets can easily contribute to oxalate accumulation in non-renal tissues even though the kidneys are healthy and their handling capacity is not exceeded.

The formation of oxalate micro-crystals is especially common in human thyroid gland and breast tissue<sup>35,36</sup>. A study of 182 normal thyroids found that

eighty-five percent of people over age 50 have calcium oxalate crystals in their thyroid gland<sup>37</sup>. This pathology has not been explained. Bio-accumulation in humans probably reflects the ubiquity of excessive oxalate in normal diets<sup>38-40</sup>. Oxalate has also been noted to cause pathological calcification<sup>41-43</sup>, weakened bones<sup>44-46</sup> and connective tissue<sup>47-49</sup>, tooth mobility<sup>50-54</sup>, and interfere with tissue healing<sup>55</sup> and promote fibrosis<sup>41,56</sup>.

Regardless of accumulation in the body, exposure to ionic oxalate has deleterious effects, including loss of calcium and electrolyte imbalances<sup>57</sup>. Castellaro, et al. (2015) demonstrated that chronic exposure of ionic oxalate alters breast cells, transforming normal breast cells to tumor cells<sup>58</sup>. Many case studies also note oxalate-induced central nervous system dysfunction without evidence of micro-crystal accumulation in the brain<sup>59</sup>. Oxalate toxicity is associated with damage to the function and structure of nerves<sup>6,60-63</sup>.

Oxalate ions and nano-crystals are increasingly implicated as a cause or aggravator of a wide range of metabolic derangements associated with chronic health issues<sup>64-66</sup>. Dramatic increases in calcium-oxalate kidney stones, and functional problems with digestive health<sup>49</sup>, neurotoxicity<sup>59,61,67-69</sup> (sleep, brain function), inflammation<sup>48,70-74</sup> (chronic pain, autoimmunity, cellular stress, fatigue, arthritis), and connective tissue instability<sup>46,73,75,76</sup> (osteoporosis, vulnerability to injury) are all consistent with increased oxalate toxicity<sup>43,77,78</sup>. Yet, these conditions (in tandem with the epidemic of insulin resistance and obesity) have led people to select foods purported to be healthier, many of which are high in oxalate.

### **Healthy food promotion, “superfoods” and lost seasonality**

Modern dietary approaches, especially the “real food” movement (which includes ancestral health, Paleo, and vegetarian approaches) has placed great emphasis on the health benefits of vegetables, nuts, and spices. Without attention paid either to nutrient bioavailability or naturally occurring toxic substances, these approaches rank foods based on assumptions that all ingested nutrients are useful to the body, which is a dubious approach to healthy food selection<sup>79,80</sup>.

Worse still, many foods with the highest oxalate content have risen to the noble status of “superfoods”, including: spinach, almonds (and most nuts), beets and swiss chard, blackberries<sup>81,82</sup>, potatoes and sweet potatoes, tea, chocolate, cinnamon, and turmeric<sup>83</sup> (see Table 1). These items are increasingly available and celebrated as healthy ingredients, even in processed and convenience packaged foods. These high-oxalate foods are now promoted through a global food system in which seasons and even seasonal pricing have been erased in the retail marketplace.

The availability of high oxalate foods we see today is unprecedented. Fresh spinach and almond-based milk-alternative beverages, for example, are now in most markets everywhere, most every day of the year. An informal survey of the grocery market place (both in national chains and in local health food stores) easily

demonstrates the proliferation of the availability of new formulations of staple foods and snack foods containing high oxalate ingredients.

This combination of “lost seasonality” and the growing popularity of neo-health food ingredients is especially dangerous with respect to oxalate consumption and the risk of toxicity. In this regard, the risk of harm from dietary oxalate may be more prevalent than at any other time in human history.

Academic papers suggest that consumption of oxalate typically falls into a narrow range of 100—150 or 100—200 mg daily<sup>84–87</sup>. These results tend to be based on small convenience samples. The authors do not describe dietary specifics, do not question the data or methods from which these estimates were derived, and do not discuss how these estimates may or may not be generalizable to other populations. These ranges also do not reflect the current food trends popularizing foods rich in oxalate. Estimating narrow ranges is unlikely to be useful in any case, as intake varies widely and we lack quality data supporting specific estimates.

Definitive, blanket statements about average oxalate intake belies both the variability and the idiosyncratic nature of food choices that can result in extremely high oxalate diets (either typically or periodically). The assumption of a steady oxalate intake level overlooks the dangers associated with the occasional ingestion of high-oxalate foods. Even a sporadic high oxalate meal (such as a spinach salad) can result in the growth of oxalate kidney stones<sup>88</sup>, and non-renal oxalate deposits as well<sup>32</sup>. Overlooking the impact of brief spikes in oxalate intake has masked the magnitude of the risks posed by dietary oxalate<sup>88</sup>.

### **Foods Containing Oxalate and Alternative Foods**

Table 1 offers an incomplete, introductory listing of popular foods that are especially high in oxalate<sup>81,82,84,89–102</sup>. Legumes, grains, fruits, and several seasonings (including black pepper<sup>82</sup>) are omitted for simplicity, though many of those also contain relatively high concentrations.

Despite crude advice often given to kidney stone patients to avoid all greens, there are many leafy greens that have low concentrations of oxalates (see Table 2)<sup>82,91,92,94,94,94,95,100,102,103</sup>. There is no benefit to a blanket prohibition on greens, especially because this over-simplified myth obscures the oxalate content of other foods such as spices<sup>97</sup>, chocolate<sup>89,94</sup>, whole grains<sup>97</sup>, potatoes<sup>91,93,94</sup>, kiwi<sup>82</sup>, figs<sup>97</sup>, and blackberries<sup>82</sup>.

**Table 1. High-Oxalate Foods Commonly Used by Health-Informed Public**

Vegetables	Nuts and Seeds	“Superfoods”
Beets	Almonds	Carob
Okra	Cashews	Chocolate; Cocoa
Plantain	Chia	Cinnamon
Potato	Peanuts	Cumin
Spinach	Pine nuts	Black Tea
Swiss chard	Poppy seeds	Green Tea
Sweet Potato	Sesame	Turmeric
Rhubarb		

**Table 2. Low Oxalate Greens**

Arugula
Bok Choy
Belgian Endive
Cabbage
Lettuce
Mâche (Corn Salad)
Mustard Greens
Watercress

**Modern Practices Increase Our Exposure and Susceptibility**

Though humans have encountered and eaten high-oxalate foods for millennia, consuming them in quantity on a daily basis threatens to overwhelm our body's ability to handle them without tissue damage, overt toxicity, and bioaccumulation. The continuous consumption we see today fails to offer time off when the body can expel accumulated oxalate, principally via the urine. The body may secondarily shunt oxalate to the colon especially when the kidneys can no longer handle the oxalate load and when the commensal bacterium *Oxalobacter formigenes* is present<sup>104</sup>.

Ubiquitous overuse of antibiotics<sup>105</sup>, food additives (especially emulsifying agents that act like detergents in the gut, scrubbing away protective mucus<sup>106</sup>), overconsumption of oxalate itself<sup>107</sup>, and other factors (known and unknown) have dramatically altered our gut microbiome and caused chronic intestinal inflammation in many people. The resulting changes in bacterial species and endothelial health in the human colon may increase absorption of oxalate and diminish our ability to excrete oxalate<sup>108</sup>. And, the chronic intestinal inflammation allows for higher rates of oxalate absorption into the body, which occurs by simple diffusion<sup>109,110</sup>. Another modern assault to gut health, bariatric surgery, has created a new and growing class of people with special susceptibility to oxalates due also to increased absorption<sup>111-113</sup>. Gastrointestinal lipase-inhibiting weight-loss drugs, especially Orlistat, also increase oxalate absorption<sup>114</sup>.

Our kidneys naturally have an impressive but limited capacity to excrete oxalates. Modernity poses threats to our kidney health through the hazards of drug- and toxin-induced kidney damage<sup>115</sup>, and the overconsumption of sugar-sweetened soda<sup>116,117</sup> and fructose<sup>118-120</sup>, sub-par intake of potassium<sup>121-123</sup> and calcium<sup>124</sup>, and insulin resistance<sup>125</sup> and the dietary and lifestyle conditions that lead up to it. Oxalate itself is a major source of kidney damage that makes it easier for oxalate to get stuck in the kidney causing a vicious cycle<sup>126-128</sup>. Renal damage, regardless of

the cause, lowers the efficiency of oxalate excretion and increases the likelihood of both renal and non-renal tissue damage from oxalate<sup>129</sup>.

### **Bioaccumulation of Oxalate**

One study using 50 gm of plain chocolate containing 55 gm of oxalate<sup>130</sup> (about 65% soluble<sup>94</sup>) demonstrated that an ordinary dose of dietary oxalate, although transient, can “trigger” a 235% increase in oxalate excretion, to levels found in PH cases. This level of exposure is enough to incite temporary renal “failure” and establish oxalate deposits in renal<sup>34,131</sup> and in non-renal tissues alike<sup>32,33</sup>. This occurs even when plasma oxalate values are within the normal range and kidney function is good. Oxalates are known to collect at sites of inflammation<sup>132</sup> and injury<sup>133</sup> where they delay healing or cause further damage. Attachment at sites of injured, inactive, stagnant tissue evades cellular clearance mechanisms, allowing minute deposits to grow and serve as sites of ongoing accumulation, owing to semi-continuous occurrence of oxalate in body fluids.

Yet, oxalate sequestered in tissues likely retains the potential to be released later (by liposomal digestion, in non-alkaline tissues) when oxalate consumption goes down<sup>134,135</sup>. But in today’s food market, neither a “low-oxalate season” nor times of food scarcity have been seen in many decades. Under these conditions, cell damage may be inevitable and especially in connective tissues.

### **Symptoms of Oxalate Toxicity**

Oxalates can trigger inflammasome reactions that may confuse our immune systems and lead to autoimmunity<sup>78,136,137</sup>. They impair bone health<sup>138,139</sup> as well as neurological<sup>68,140</sup>, cardiovascular<sup>41–43</sup>, and kidney function<sup>12,141,142</sup>.

The symptoms of oxalate toxicity can be very hard to identify primarily because the patterns vary in idiosyncratic ways from person to person<sup>7</sup>. They are often subtle, typically affect multiple body systems, and often flare up unpredictably and irregularly—perhaps as the body tries to let go of them. These symptoms are common and non-specific (GI distress, headaches, joint and back pain) and can be vague (including generalized malaise, low energy, frequent urination). Because objective tests of urine<sup>141</sup> and tissue biopsy<sup>37</sup> are unreliable, oxalate-related symptoms go unrecognized as such. Despite several recent medical case reports that faulted the consumption of peanuts<sup>8,142,143</sup>, green juices<sup>8</sup> and smoothies<sup>144</sup>, tea<sup>145</sup>, nuts and nut butter<sup>146</sup>, cashews<sup>147</sup>, and a weight loss diet consisting of spinach, kale, berries, and nuts<sup>148</sup> for kidney failure in patients, oxalates remain obscure compounds of no special concern in modern health care.

### **Historical Diagnosis**

We didn’t always ignore this problem. Oxalate-induced whole-body illness was a recognized, although debated, condition in the 19<sup>th</sup> and early 20<sup>th</sup> centuries, known to be associated with diet and manifesting with digestive, neurological, and



rheumatic problems<sup>149</sup>. In the 5<sup>th</sup> edition of his famous 1857 textbook, *Urinary Deposits*, Golding Bird stated "... we are told... that oxalate of lime is of constant occurrence, and of no importance. A remark to which too many sufferers from this diathesis can give a melancholy denial." —5th ed., (1857), p. 217<sup>150</sup>

But, like the perpetual elusiveness of the remedy for kidney stones, associating non-renal oxalate toxicity with objective clinical tests of body fluids (especially urine) remained unsolvable. Thus, the idea of non-renal oxalate toxicity, especially when kidney function appears normal, was essentially dismissed. As a result, deeper investigations of case reports or direct experiments on humans are far too few and often flawed.

In the late 1800s and early 1900s, dietary intervention was recognized as an effective treatment for a constellation of symptoms associated with rhubarb season or with poor oxalate metabolism. The early knowledge has slipped into obscurity, awaiting rediscovery by a funding- and fad-driven research environment and a medical paradigm that in the early 20<sup>th</sup> Century decisively decomposed the human body into isolated body parts and systems. In the nutrition sciences, especially in epidemiology, preconceived cultural notions dominate and limit the questions researchers are willing to investigate. For example, toxicology data on naturally occurring plant toxins is very limited. As toxicologist Gerrit Speijers puts it:

"Perhaps the hesitation to imply the safety aspects of inherent plant toxins in the agricultural research on plant breeding, fed by the fear that important and valuable plant foods would become a perceived health risk, has also contributed to the backlog in knowledge of the inherent plant toxins." —Speijers (1995), p. 224<sup>79</sup>.

### **Side-Stepping the Trigger/Maintenance Processes with Diet**

Once the body is retaining oxalates, lowering oxalate intake consistently to the expected average intake of around 100-150 mg per day may not be enough to reverse the damage, although research in this area is lacking. Vermeulen's Trigger and Maintenance theory<sup>131</sup> and many anecdotal reports (and the very definition of a low oxalate diet) indicate that intake must go below this "maintenance" exposure to a level that permits the destabilization and clearance of deposits and eventual tissue recovery. This trigger/maintenance response suggests that controlling and reversing oxalate toxicity in people who have become "accumulators" requires lowering oxalate levels in the diet to under ~60 milligrams a day. For reference, a half cup of cooked spinach contains several hundred milligrams of oxalate (330 – 520 mg)<sup>82,90,94</sup>.

There are many therapeutic and preventive benefits of avoiding dietary oxalates, including improvements in kidney function<sup>87,88,146,151-154</sup>. In addition, both published and unpublished reports suggest benefits such as reversal of

neurotoxicity (brain fog, cognition, behavioral and mood disorders, and sleep improvements<sup>155</sup>), recovery of connective tissue stability<sup>89,156</sup> and reduced symptoms of autoimmunity<sup>136</sup>.

However, with improved kidney function, tissue stores of oxalate can be mobilized (as has been observed after kidney transplants in primary hyperoxaluria (PH) patients<sup>157,158</sup> and in the symptoms reported by thousands of low oxalate dieters without PH<sup>155</sup>). Even when tissue clearance of oxalate from the body provokes on-going periodic elevated oxalate excretion, improved kidney function is evident<sup>153,154</sup>.

The safety of the oxalate release process depends, in part, on the rate of release not exceeding the body's alkaline buffering capacity and kidney tolerance. Even when within metabolic capacity, periodic elevated circulating oxalate is likely to cause temporary symptom "flare-ups" with the potential to damage kidneys, the vascular system and other tissues during "clean-out" phases. There is also some evidence among PH patients that events such as surgery/surgical recovery<sup>49</sup>, lithotripsy<sup>159</sup>, and giving birth<sup>160</sup> may mobilize oxalate from previously quiescent internal deposits<sup>161,162</sup>. Similarly, acute oxalate nephropathy has followed non-renal organ transplantation in patients with cystic fibrosis.<sup>163</sup>

The reversal of oxalate accumulation in cases of dietary hyperoxaluria has never been formally monitored. Among PH patients, the time required for resolution of hyperoxaluria following liver and kidney transplantation varies widely. Tissues continue to release oxalate for a minimum of three years<sup>157</sup> and may carry on for well beyond seven years<sup>162</sup>. Data is limited due to the small number of PH patients, poor survival rates, and lack of long-term follow-up testing. However, these lengthy release periods are consistent with reports from individuals who have systematically followed a long-term low-oxalate diet<sup>155</sup>.

Reactions to the low oxalate diet are varied, from simple symptom relief, to serious side-effects in some cases<sup>155</sup>. An abrupt shift from a high oxalate intake to a low oxalate intake may be ill-advised due to the potential for excessive mobilization<sup>155</sup>.

### **Awareness Lacking**

Biomedical researchers, clinicians, and the public health workforce have virtually no awareness of the threat of biological toxicity posed by over-exposure to oxalate. As a result, oxalate in plants (as well as other natural toxins) are overlooked as a potential problem associated with a number of popular foods. Ignorance of oxalate toxicity may pose an enormous, hidden, and growing threat to public health.

Unfortunately, neither dietary professionals nor the consuming public are aware of the presence or dangers of oxalates in familiar and trusted foods. Even lists of oxalate content from the USDA and major universities offer very incomplete data that is riddled with errors<sup>89,164</sup>.

Encouragement of consumption of high-oxalate foods could lead to increased morbidity, not less as is claimed and desired. This is because the potential to ingest and absorb “trigger” doses and consistently eat “maintenance” doses can lead to a growing body burden of oxalate as well as constant exposure to ionic oxalate. The action we must take is to stop poisoning ourselves<sup>165</sup>. It makes no difference if the toxin is a man-made poison or one of nature’s poisons. A single toxin interfering with the function of the connective tissue, immune system, nerves, glands, digestion and elimination deserves our attention<sup>80</sup>.

### **Conclusion**

Despite the prevailing message that there is no upper safety limit for plant food consumption, not all vegetables and seeds are healthy and safe to eat on a regular basis, as toxicological studies and many case reports have proven. Sub-lethal exposure to oxalate contributes to disease, although we typically overlook the non-lethal effects and the non-renal effects<sup>166</sup>.

The basic logic of biology tells us that the two biggest drivers of illness are toxicity and deficiency. Regular and repeated exposure to a toxic substance is harmful. Plants are inherently toxic; even food plants retain varying degrees of toxicity. However, this notion is foreign to the general public and health professionals alike.

In today’s bifurcated food world dominated by sugary, nutrient-poor convenience foods opposed by super-charged “health” foods featuring high-oxalate ingredients, the overall health outlook remains ominous. The promotion of high oxalate foods is likely to have the opposite of the intended effect. Rather than making us healthier, the superfood craze could be, not unlike the holy war against saturated fat, launching another public health calamity, as expensive and unpleasant as the current diabetes and obesity explosion. Those of us promoting healthy eating owe it to ourselves, and to those we hope to help, to get informed about oxalate toxicity, and to embrace dietary strategies that enable us to avoid and ultimately recover from it.

“From a practical point of view, it would be better to avoid oxalate-rich foods [...], especially when other sources of green vegetables are available.” —Hoover and Karunairatnam (1945)<sup>57</sup>

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