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# Castor Oil: New Lessons from An Ancient Oil

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**Castor oil, from *Ricinus communis,* has been used since ancient times as a safe and reliable laxative. The pharmacologically active molecule in the oil is ricinoleic acid. This hydroxylated, long-chain fatty acid has multiple effects on the intestinal mucosa, resulting in fluid secretion. Early studies indicated that the mucosal effects were due to enteritis or interference with cellular metabolism. Later studies revealed that the fatty acid could increase mucosal permeability and cause cytotoxicity, associated with release of eicosanoids, platelet activating factor, other autacoids and nitric oxide. In addition, ricinoleic acid disrupts normal intestinal motility. The combination of these effects on the mucosa and smooth muscle of the gut account for its laxative action.** © **1998 John Wiley & Sons, Ltd.**

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## INTRODUCTION

The most widely used laxatives are derived from botanical sources. Among these, castor oil holds a special place in history (see Gaginella *et al.*, 1975 for historical references). The first prescriptions for castor oil may well have been written in pre-Christian times. Early Egyptian physicians employed the *Ricinus communis* (Euphorbiaceae) plant for medicinal purposes. It is said that the seeds of the plant were chewed with beer as a remedy for constipation.

*Ricinus communis* is indigenous to many parts of the world, especially the tropics and the Mediterranean. The plant was called *Kiki* by the ancient Greeks and *Palma Christi* by the Romans, because of the resemblance of its leaves to the palm of the hand. In the Americas a variant of *Ricinus communis* was used by the Aztecs for constipation. In the 17th century, various medical authors referred to what probably were seeds of the *Ricinus* plant as 'seeds of spurge', 'great spurge' and 'purgative beans'. During this era formularies include reference to 'castor' oil. The name *castor* derived from the Jamaican plant *Agnus castrus* a variety claimed through folk lore to reduce sexual appetite.

The consensus among many 18th century practitioners was that an 'acrid principle' was the active laxative ingredient in castor oil, or that its effect was due to contamination by cortical material from the *Ricinus* seeds. The oil expressed from the whole seeds was known to be more potent than oil obtained by cold-pressing the decorticated seeds. Chemically, castor oil was noted to have different characteristics than other vegetable oils such as olive oil. By mid-1800, ricinoleic acid was identified as the major component of castor oil. More specifically, ricinoleic acid is an 18-carbon monounsaturated (position 9–10), 12-hydroxylated aliphatic fatty acid. However, the chemical structure of ricinoleic acid (as its salt, ricinoleate) imparts amphipathic (surfactant) characteristics to the molecule, accounting for its ability to alter membranes and interact with cellular enzymes. This seems also to be the clue to ricinoleate's relatively non-specific effects on the intestinal mucosa.

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## EARLY PHARMACOLOGICAL STUDIES

Perhaps the first 'modern' pharmacological study on ricinoleate was done by Meyer (1890). He confirmed that about 90% of castor oil consisted of the triglyceride of ricinoleate and that this fatty acid was responsible for the laxative effect of the oil. Although early investigators noted watery stools after castor oil or ricinoleate, it was assumed that the effect was due mostly to increased motility of the intestine. Some enlightened observers, however, commented that, '*…the extremities of the arteries and excretory vessels belonging to the glands are opened by the sharp and aperient qualities of the purgatives, unlocking the secret pores of the inward coat of the intestines…*' (see Brandreth, 1867). Several authorities of the time, described purgative/laxative action as due to '*…stimulating exhalant vessels terminating in the inner coat of the intestines and mouths of the excretory ducts of the inner mucous glands, by which an increased flow of serous fluid takes place…*' and '*…stimulating the neighboring viscera, … so as to produce more copious flow of their secretions into the intestines'.*

The 20th century brought continued use of castor oil and further investigations into its mechanism of action. By the 1930s it was noted that sodium ricinoleate was not absorbed by the intestinal mucosa, '*…hence any action it may exert should be limited to the lumen of the intestinal*

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*canal*' (Myers *et al.,* 1933). Watson and Gordon (1962) subsequently reported that small doses of castor oil were completely absorbed and did not produce a laxative effect; larger doses were incompletely absorbed and did produce the laxative response. These findings sparked contemporary clinical researchers to examine the aetiopathophysiology of steatorrhea, a condition characterized by watery diarrhoeal stools containing undigested fats. The investigators hypothesized that the diarrhoea in these patients might be due to the endogenous formation of a poorly or non-absorbable fatty acid similar to ricinoleic acid. Indeed, chemical analysis revealed the presence of hydroxylated fatty acids in the stool of the patients with steatorrhoea (Webb *et al.,* 1963). These findings renewed scientific interest in castor oil (ricinoleic acid), which then served as a model for investigating the mechanism(s) for the occurrence of watery stools in the patients with steatorrhoea (Gaginella and Phillips, 1975).

## CONTEMPORARY PHARMACOLOGY OF CASTOR OIL

We know that, in amounts liberated from a laxative dose of castor oil, ricinoleic acid alters intestinal motility and mucosal transport of water and electrolytes. Relatively few investigations have been done on ricinoleate's effects on motility. It is generally believed that the mucosal/fluid transport effects of ricinoleate dominate in the laxative response.

The rhythmic pattern of electrical activity that drives the coordinated movement of intraluminal contents through the gut is altered by castor oil. Contrary to popular belief, castor oil does not generally stimulate intestinal motility. Rather, it disrupts small intestinal electrical and circular muscle contractile activity, and inhibits motility in a variety of *in vitro* and *in vivo* experimental models (Gullikson and Bass, 1984). The functional result of the experimental effects on the circular muscle is less segmentation (restriction to aboral flow) and thus facilitation of transit of stool to the colon. In addition to evoking fluid accumulation in the intestine the increased rate of transit through the gut will be further compromised. In man, if $>6$ L/24 h of fluid reaches the colon, the colon's capacity for reabsorption may be exceeded and laxation/diarrhoea is likely to occur.

Ricinoleate inhibits fluid absorption and activates secretion in many species, including man (Phillips and Gaginella, 1977; Gaginella and Bass, 1978; Capasso and Gaginella, 1997). The effect on fluid accumulation is associated with the poor intestinal absorption of ricinoleate (Ammon *et al.,* 1974). This confirmed findings of poor absorption of castor oil repeated by Meyers (1933) earlier. Ricinoleate does not evoke luminal fluid accumulation in canine extrinsically denervated intestinal loops (Kelly *et al.,* 1981) or intestinal loops isolated from the circulation (Gadacz *et al.,* 1976), giving support to a luminal locus of action. In rats, a reflex mechanism involving the myenteric plexus has been proposed to account for the secretory effects of ricinoleate (Karlstrom 1986).

The effects of ricinoleate are associated with mucosal injury. A variety of enzymes and metabolic systems are also affected by ricinoleate. Whether detrimental effects of ricinoleate on epithelial cell metabolism precede mucosal damage, or physical injury to the mucosa causes the negative metabolic consequences, is not known. *In vitro,* ricinoleate inhibits the sodium–potassium pump (Phillips *et al.,* 1965), oxidative metabolism (Nakao, 1963; Gaginella *et al.,* 1975), active alanine transport (Hajjar *et al.,* 1979) and adenylyl cyclase (Gaginella *et al.,* 1978) in preparations of rodent intestine. More than 50 years ago Valette (1936) showed that ricinoleate was cytotoxic to rat intestinal mucosa *in vitro.* Ricinoleate is also cytotoxic to suspensions of hamster intestinal cells (Gaginella *et al.,* 1977b).

In 1958 Reynell and Spray reported that castor oil produced 'chemical gastroenteritis' in rats. Castor oil also produced colitis in ponies after oral administration (Johnson *et al.,* 1993). Perfusion of hamster small intestine with 2 mM ricinoleate caused mucosal injury with an increase in permeability of the luminal barrier (Cline *et al.,* 1976; Gaginella, *et al,* 1977a). Additional studies by scanning electron microscopy (Gaginella and Phillips, 1976) and function (Gaginella *et al.,* 1977a; Gullikson *et al.,* 1977; Bretagne *et al.,* 1981) confirmed that ricinoleate causes mucosal injury. Ricinoleate or castor oil release endogenous mediators of intestinal secretion (Capasso and Gaginella, 1997), including kinins (Autore *et al.,* 1990), platelet activating factor (Pinto *et al.,* 1989; Mascolo *et al.,* 1993) and eicosanoids (Capasso *et al.,* 1987; Gaginella, 1990). Ricinoleate may also act on epithelial cell membranes as a calcium ionophore (Maenz and Forsyth, 1982) and/or a blocker of chloride ion channels (Hwang *et al.,* 1990).

Although the details are still incomplete, the free radical nitric oxide (NO) is believed to be important in gastrointestinal function. Under some circumstances it may protect the mucosa from damage while in other instances it seems to mediate mucosal damage (Miller and Gaginella, 1995). A series of experiments evaluated the involvement of NO in the action of castor oil. Using inhibitors of NO synthase, Mascolo *et al.* (1993) showed that NO was involved in castor oil-induced diarrhoea in rats. NO stimulates electrolyte secretion *in vitro* (Tamai and Gaginella, 1993). Subsequent studies showed that it was possible to dissociate the diarrhoea from the mucosal injury produced by castor oil (Capasso *et al.,* 1994). The rationale to justify the dual action of castor oil arises from that fact that there are multiple isoforms of NO synthase, including cNOS (constitutive, may be protective) and iNOS (inducible, possibly injurious). If one assumes that NO derived from iNOS is involved in provoking secretion, *independent of epithelial cell injury*, then inhibition of iNOS would block the secretion. However, if tissue damage is also accompanied by an increase in NO, the NO in may initiate protective or restitutive mechanisms—over the same time period that it also activates electrolyte secretion. Nonselective blockade of all NO production would attenuate the secretion while at the same time preventing the 'protective' effect of the NO.

In conclusion, castor oil has provided mankind with a safe and effective natural laxative with a rich history. Its influence on multiple processes involved in intestinal mucosal function, has frustrated scientists who would dare to assign a definitive mechanism of action to castor oil. This ancient oil has led many on an interesting journey, always revealing new paths to explore. We can continue to expect that more lessons will be learned from castor oil, a simple yet widely useful gift from nature.

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