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Review or Mini-review

The toxicology mechanism of endophytic fungus and swainsonine in locoweed

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ABSTRACT

Locoweed is a perennial herbaceous plant included in *Astragalus* spp. and *Oxytropis* spp. that contains the toxic indolizidine alkaloid swainsonine. The livestock that consume locoweed can suffer from a type of toxicity called *locoism*. There are aliphaticnitro compounds, selenium, selenium compounds, and alkaloids in locoweed. The toxic component in locoweed has been identified as swainsonine, an indolizidine alkaloid. Swainsonine inhibits lysosomal a-mannosidase and mannosidase II, resulting in altered oligosaccharide degradation and incomplete glycoprotein processing. Corresponding studies on endophytic fungi producing swainsonine have been isolated from a variety of locoweed, and these endophytic fungi and locoweed have a close relationship. Endophytic fungi can promote the growth of locoweed and increase swainsonine production. As a result, livestock that consume locoweed exhibit several symptoms, including dispirited behavior, staggering gait, chromatopsia, trembling, ataxia, and cellular vacuolar degeneration of most tissues by pathological observation. Locoism results in significant annual economic losses. Therefore, in this paper, we review the current research on locoweed, including that on locoweed species distribution in China, endophyte fungus in locoweed, the toxicology mechanism of locoweed, and the swainsonine effect on reproduction.

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1. Introduction

Locoweed (*Astragalus* spp. and *Oxytropis* spp.) is a perennial flowering plant found frequently in the rangelands of the western United States, Asia, and South America. It is one of the most poisonous weeds and harms grassland and animal husbandry development worldwide. Specifically, locoweed is distributed mainly in the United States, Canada, Mexico, Russia, Spain, Ireland, Morocco, and Egypt and is most serious in the western United States (Chen et al., 2011). In China, it is distributed mainly in Inner Mongolia, Ningxia, Gansu, Qinghai, Xinjiang, Tibet and other regions. Currently, locoweed has not only caused the deaths of a large number of livestock, decreased livestock breeding, and inhibited the improvement of livestock, but has also done great harm to the sustainable development of local animal husbandry. Locoweed is divided into three types, selenium, nitro compound, and swainsona. A large number of studies on locoweed, along with deepening study of it, have found that locoweed's main toxin is active substances in swainsonine (Daniel and Michae, 2009; Welsh, 2007; Wang et al., 2007). American researchers with Braun (Braun et al., 2003) obtained swainsonine production from *M. anisopliae* in 1985. The researchers think these show a very close relationship between endophytic fungi and swainsonine in locoweed. Subsequently, many scholars have isolated endophytic fungi, producing swainsonsine in various kinds of locoweed.

Swainsonine, a trihydroxy indolizidine alkaloid, is the main toxic component in locoweed. The structure of the swainsonine cation is similar to the structure of mannose, and it has a higher affinity than mannose for mannosidase. Swainsonine is a well-known inhibitor of lysosomal a-mannosidaseand Golgi mannosidase II. Poisoning induces enzymatic dysfunction and the accumulation of complex oligosaccharides in lysosomes; therefore, swainsonine has a significant inhibitory effect on a-mannosidase in lysosomes, and it inhibits glycoprotein synthesis and the production of a mixture of mannose and asparagine polysaccharide, resulting in vacuolation in different cells, especially in neurons (Wu et al., 2014a,b). Earlier studies demonstrated that natural or experimental long-term ingestion of swainsonine-containing plants causes serious disorders in reproductive functions of livestock (cattle, sheep, horses, and goat), including failure to conceive, early embryo loss, or abortion, which result in great economic losses in the livestock industry (Panter et al., 1999a,b). In vivo studies of pregnant and nonpregnant animals, such as cattle, sheep, and goats, showed that ingestion of swainsonine-containing plants can decrease serum progesterone concentration and subsequently disrupt ovarian function, accompanied by delayed estrus, increased estrous cycle length, delayed conception, and abortion (Panter et al., 1999a,b; Tong et al., 2008). However, the role and mechanism of locoweed in vivo is unclear and calls for further research. This paper mainly examines the current research trends regarding locoweed species distribution in China, endophyte fungal in locoweed, the toxicology mechanism of locoweed, and the swainsonine effect on reproduction.

2. The distribution of locoweed in China

Locoweed (*Astragalus* spp. and *Oxytropis* spp.) is a perennial flowering plant found frequently in the rangelands of the western United States, Asia, and South America. Locoweed poisoning is related to animal production performance indicators, including the feed conversion rate, weight, susceptibility to other diseases, and reproductive capacity. These indicators can be used to assess the economic consequences of locoweed poisoning and develop effective management measures to reduce losses (Wu et al., 2014a,b). Economic losses due to toxic poisoning from plants total more than US340 million in the western United States every year (Zhou et al., 2013). The consumption of locoweed by cattle, sheep, and horses induces a neurological condition called locoism. Locoweed causes livestock death and damages livestock breeding in addition to causing grassland degradation and reductions in pasture usage. Locoweed is one of the most serious poisonous weeds, damaging grassland animal husbandry production and development worldwide (Braun et al., 2003; McLain-Romero et al., 2004). According to statistics, the hazard area of natural grassland, 33.3 million hm^2, in which the main poisonous weed is locoweed, accounted for approximately 33% of the damage area of poisonous weeds in China. At present, there are 44 types of locoweeds, and among these, 15 species are serious grassland hazards. These hazardous weeds are mainly distributed in Inner Mongolia, Gansu, Qinghai, Tibet, and Xinjiang in China. Locoweed poisoning costs billions of RMB from direct or indirect economic losses in China each year (Shi, 2001). Information about different locoweed species in western grasslands in China appears in Table 1* (Wu et al., 2014a,b). Locoweed is mainly distributed over the altitude of 1000 m, and located in the dry and half dry regions. Locoweed has the characteristics of drought resistance, cold tolerance and strong vitality (Table 1).

3. Endophyte fungus in locoweed

3.1. The poison of locoweed

Locoweed toxin is an alkaloid that can be divided into two classes according to the characteristics of its chemical structure: indolizidine alkaloids and quinolizidine alkaloids that represent the swainsonine and swainsonine *N*-oxide, separately; and quinolizidine alkaloids that represent anagyrine, thermopsine, *N*-Methylcytisine, sparteine, and so on. Which kinds of alkaloids contain the main toxicity composition in locoweed? Also experienced a relatively long process to determine the major composition of the toxicity locoweed. By making an animal model of locoweed poisoning, we observed the typical symptoms of poisoning and detected physiological and biochemical indicators of blood and pathological changes in organization. The main toxic component of locoweed is swainsonine; this point has been accepted by most scholars in the academic discussion of swainsonine and glycosidase inhibitor; swainsonine is the only reason for the symptoms of locoweed poisoning (Li et al., 2005).

3.2. Endophytic fungus and swainsonine

Researchers originally thought sources of swainsonine in locoweed were a kind of metabolic product in the process of locoweed growth, but in later studies, newer research has estasblished that the element content of swainsonine in locoweed is closely associated with endophytic fungus. In 2003, Braun (Braun et al., 2003) isolated *Ambellisia* strains from locoweed plants, cultured by fermentation in vitro, and detected swainsonine from its metabolites and endophytic fungus in legume plants was isolated from locoweed plants for the first time. Braun also reported that locoweed had a high content of swainsonine, which was also high in fungal endophyte. This showed that endophytic fungus in locoweed can affect the content of swainsonine. The number of fungal endophytes in locoweed and its growth status would affect the output of swainsonine. McLain-Romero et al., 2004 got endophytic fungus from the leaf, stem, flowers, and seeds of *O. sericea*, *A. mollisimus*, and *O. lambertii*, and they can produce swainsonine under conditions of artificial culture. Creamer et al. (2007) researched the correlations of locoweed swainsonine between endophytic fungus and locoweed, and they found that the correlation of swainsonine of *O. lambertii* and endophytic fungus of locoweed is very strong,