neo neaster

Manna of Cotoneaster

The purgative manna is white, slightly yellowish, round pieces with a very sweet taste and cooling properties produced by Cotoneaster genus of Rosaceae Family. It is called **Shir-e-Khesht** in Iranian traditional medicine. This sweet substance has been mentioned frequently in well-known traditional medicine books like “Canon of Medicine” by Avicenna, “Alhavi” by Rhazes, and “Makhzan-ol-Advieh” by Aghili Khorasani[1].

In the Iranian traditional medicine, it has been repeatedly prescribed as a bile laxative, appetite enhancer, purgative, astringent, expectorant, biliousness, tonic for the liver[2].
Major component of purgative manna are **Carbohydrates,** including mannitol, fructose, glucose, sucrose and polysaccharide fractions, which causes **osmotic diarrhea.**
The chemical compositions of Cotoneaster species were analyzed by HPLC and it do contain Hyperoside, Ursolic acid and Chlorogenic acid complexed to carbohydrate chains. These **Polyphenolic and Flavonoid compounds** have excellent **antioxidant** activity, which protects hepatocyte against oxidative stress[3].
Furthermore, manna of cotoneaster has high nutritional values by containing large amount of **Essential trace element such as zinc and copper.** This trace elements play major role in normal growth, brain development, behavioral response and bone formation of neonates[4].

Neonatal jaundice

Neonatal jaundice is the primary reason for re-admission and hospitalization during the neonatal period[5]. Around 60% of full-term neonates and 80% of preterm neonates show signs of jaundice within 2–5 days after birth[6, 7].

Conventional therapy

The conventional therapy for neonatal jaundice is phototherapy. If the level of bilirubin exceeds the risk level, exchange transfusion (ET) is used as the last resort to reduce bilirubin[8]. Although these therapies have favorable outcome, they are accompanied by significant side effects:

Phototherapy

Phototherapy can be harmful especially in extremely low-birth-weight (ELBW) newborns[9]. The most common side effects of phototherapy include skin complications, dehydration, fever, irritability, retinal degeneration, bronze baby syndrome, thrombocytopenia, oxidative stress-related diseases such as necrotizing enterocolitis and patent ductus arteriosus[10-13]. In addition, phototherapy is costly and, since the neonate is hospitalized and his eyes are covered, the relationship between the mother and the neonate is disturbed.

Exchange transfusion

Numerous complications including those associated with transfusion and catheter usage may also occur during different parts of blood exchange procedure. Exchange transfusion could cause complications such as hypertension, coagulopathy, vascular thrombosis, arrhythmia, sepsis and even death in neonates[14].

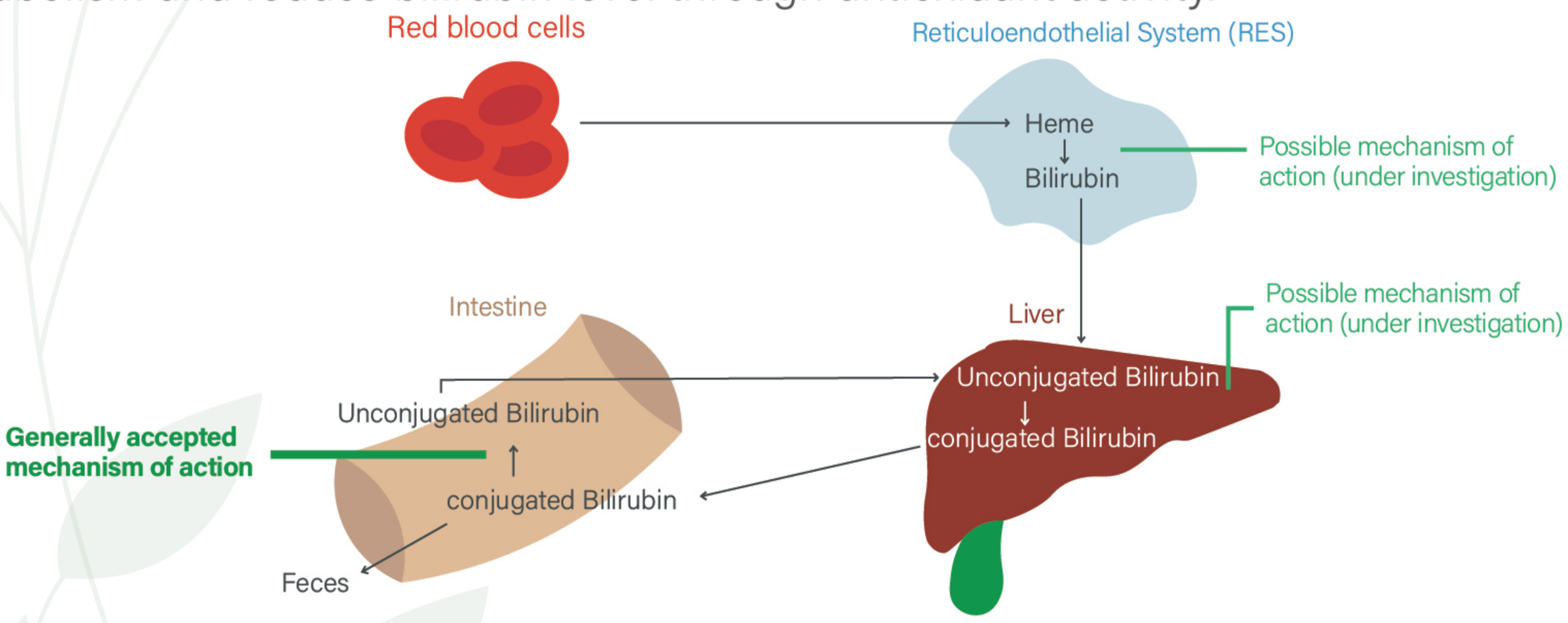
Since incidence of these side effect will increase in accordance to duration of phototherapy, other treatment methods are investigated to decrease the duration of phototherapy, reduce the chance of ET in neonates and reduce the cost of treatment.

Mechanism of Purgative Manna

The effect of Purgative Manna on neonatal jaundice has been attributed to several factors[15]:

1. The laxative effect of Purgative Manna is due to mannitol which as the main source of sugar in Purgative Manna can lead to increased intestinal transit and more bilirubin excretion in the gastrointestinal tract of neonates to reduce enterohepatic cycle.

2. Bonding of some components of Purgative Manna with bilirubin prevents the introduction of bilirubin into the enterohepatic circulation (intestinal-liver cycle) and reduces neonatal jaundice. Moreover, it is possible that flavonoids in Purgative manna affect the bilirubin metabolism and reduce bilirubin level through antioxidant activity.



Recent studies on Manna of Cotoneaster

Table 1 from show results of clinical studies performed on purgative manna. These studies mostly confirm the efficacy of purgative manna on the alleviation of Neonatal jaundice[16]:

Clinical Trial type	Intervention (type, dose, duration)	Result on neonates	Reference
Double-blind, placebo controlled	Oral, 100 case neonates (<1 mo.) (5 drops, 3 times/day, for 5 days)	Treating 80% infants after 2.5 days with the combined treatment of phototherapy and Cotoneaster drops	Azadbakht et al. (2015a)
Double-blind, placebo controlled	Oral, 100 case neonates (<1 mo.) (5 drops, 3 times/day, for 5 days)	The rapid reduction of serum bilirubin after spending 3 day treatment of purgative manna	Azadbakht et al. (2015b)
Double-blind, placebo controlled	Oral, 50 case neonates (6 g/ 8 ml water for 3 days)	No significant effect of Cotoneaster drops in treating NJ	Farhat et al. (2006)
Double-blind randomized controlled	Oral, 60 case neonates, 3 to 10- day-old (30 ml containing 5.0 g Cotoneaster, 3 times/day, for 1.5 days)	The rapid reduction of jaundice along with decreasing the hospitalization length	Ghotbi et al. (2006)
Double-blind, placebo controlled	Oral by mothers and 120 case neonates (3 drops, 3 times/day, for 1.5 days); 9 drops for mothers under the same conditions	A remarkable and quick reduction of serum bilirubin and length of hospitalization the jaundice reduction in infants fed with milk of mothers consuming billinaster drop	Khoshdel and Kheiri (2011)
Double-blind randomized controlled	Oral, 70 case neonates, 3 to 5- day-old (5 drops, 3 times/day, for 3 days)	No significant impact of Cotoneaster drops at the administration dose in treating NJ	Mansouri et al. (2012)
Single-blind randomized	Oral, 70 case neonates, 3 to 7- day-old (5 drops/kg, 3 times/ day, for 2 days)	High-efficient, safe treatment of neonatal hyperbilirubinemia by Cotoneaster drops	Fallah et al. (2014)
Randomized controlled	Oral by mothers and 60 case neonates, 2 to 23-day-old (3 drops/kg, 3 times/day, for 3 days); mothers received the drops three times over their neonates	A faster decrease in NJ with consumption of cotoneaster by both mothers and neonates with a decreased hospitalization duration.	Rafieian-Kopaei et al. (2016)
Randomized controlled	Oral, 98 case neonates, 2 to 14- day-old (5 drops/kg, 3 times/ day, for 2 days)	A significant decrease in the total and direct bilirubin levels using the combined effect of bilineaster drop and phototherapy	Ameli et al. (2017)
Randomized controlled	Oral, 24 case neonates (3 drops/kg, 3 times/day, for 3 days)	No notable effect of Cotoneaster drops in treating jaundice in neonates under phototherapy	Rahani et al. (2017)
Double-blind randomized controlled	Oral, 222 case neonates, 4 to 14-day-old (5 drops/kg, 3 times/day, for 3 days)	A 75% decrease in the risk of occurrence of severe jaundice in the Purgative Manna group compared to the placebo group	Fakhri et al. (2019)

Three Systematic Reviews and Meta-analysis evaluated the effect of purgative manna on neonatal jaundice. All three studies found that purgative manna administration reduced bilirubin levels at 12,24,36,48 and 72 hours following treatment and decreased the length of hospital stay[17-19]. These Systematic Reviews has also found that combined use of purgative manna and phototherapy has considerable effect on decreasing duration of phototherapy which consequently decrease any possible side effects of phototherapy[18].

3 / Mechanism of Purgative Manna

In addition, by staying less time in hospital, the cost of hospital stay and anxiety of parents will be reduced. Figure 1 and 2 demonstrate mean difference in bilirubin level at 36 hours and length of hospital stay in days[18]. No significant side effects were reported in neonates during hospitalization and follow-ups.

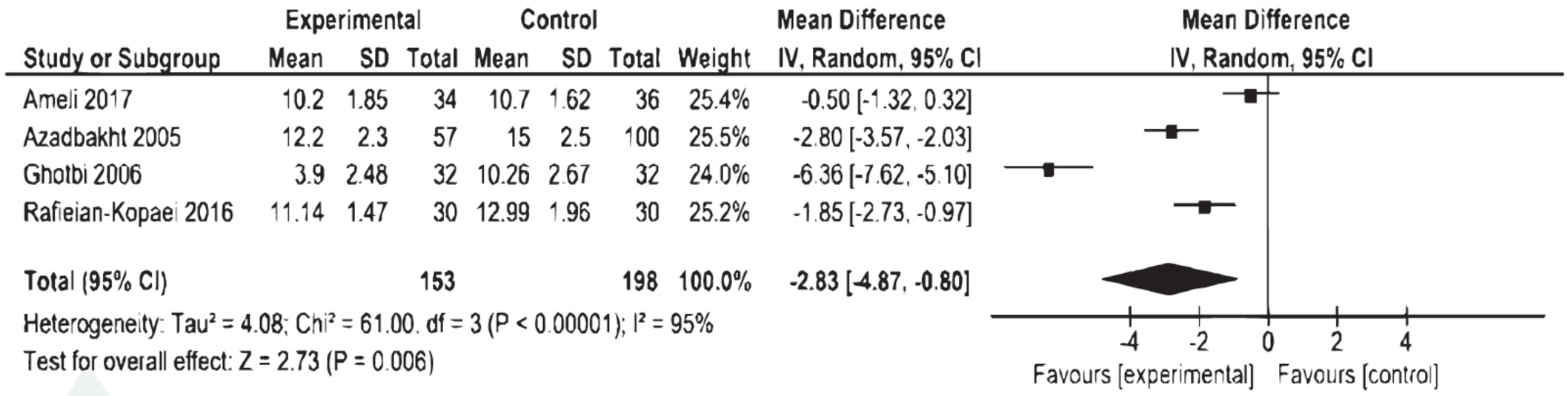


Figure 1. Comparison of bilirubin level at 36 h.

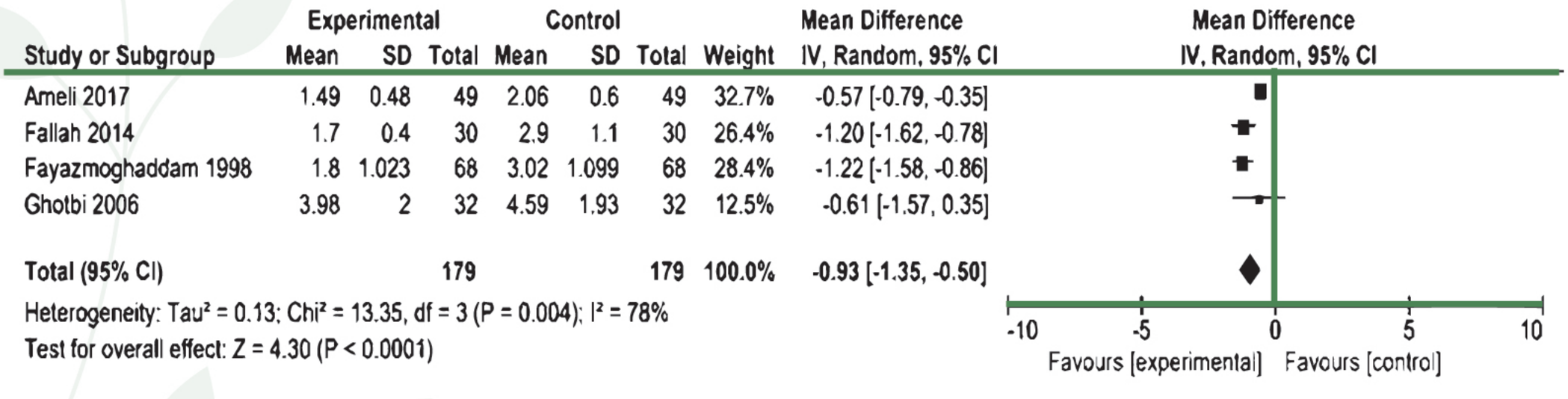


Figure 2. Comparison of length of hospital stay in days.

However, some clinical studies report the effect of cotoneaster drops in neonates to be insignificant. Several reasons may cause these contrast of results:

(I) Design, implementation and statistical analysis flaw such as low administered dosage, small sample size, frequency and duration of purgative manna administration[16].
(II) Higher level of mean bilirubin in study group can diminished efficacy ratio of purgative manna to negligible amount[16].
(III) Assessment of the bias risk of many studies using different tool such as "the Cochrane Collaborations' tool for assessing risk of bias" has demonstrated high Selective reporting (reporting bias) and Random sequence generation (selection bias)[18, 19].
(IV) Most studies have used available products of manna in market. Unfortunately, many of these products contain less than a standard amount of manna which is needed to induce therapeutic effect E.g., some studies had reported no difference in frequency of defecation upon use of purgative manna products which in turn can point to low Quality of available products[20].

NEONEASTER®

NEONEASTER® is a natural product formulated with unique method from manna of cotoneaster species in order to treat neonatal jaundice and manage constipation.
NEONEASTER® has standardize with 300mg/ml Mannitol as active component.
Novelty in the formulation of NEONEASTER® has resulted in **More Efficacy** and **Stability** with **Less Side Effects** compared to other available products in the market.
Several large scaled comparative research is being conducted on NEONEASTER® and other available product of manna of cotoneaster in market. For example, Evaluation of acute and sub chronic toxicity and colitis of NEONEASTER® in rats. The project received approval from institutional research ethics committee of Tehran university of medical sciences on July, 2021 and was found to be in accordance to ethical principal and national norms and standards conducting medical research in Iran (Approval ID: IR.TUMS.VCR.REC. 1400.098).
A large sample multi-Centre clinical trial is also going to be run in 2022 in order to compare effect of NEONEASTER® with other available product of manna of cotoneaster in market.
In **Post Marketing Surveillance (PMS)**, ARAS pharmaceutical will continuously and rigorously monitor NEONEASTER® in market in order to ensure its safety, record any possible side effect in special populations and provide further information about NEONEASTER®.

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